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24 NOV 2016

[redacted]
Policy and Risk Adviser
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Ref: H201604318

Dear [redacted]

Response to your request for official information

Thank you for your request of 27 October 2016 under the Official Information Act 1982 (the Act) for

> *"Can I have a copy of this referred to in the minutes...*
> *This paper summarised the efficacy and safety of Gardasil 9 identified from the marketing authorisation studies."*

The information relating to this request is itemised below, with copies of documents attached.

Request	Response
Can I have a copy of the paper summarising the efficacy and safety of Gardasil 9	Attached is: *1. The paper: National immunisation schedule change to Gardasil 9 as a 2 dose schedule for boys and girls*

I trust this information fulfils your request.

Yours sincerely

[redacted]

Group Manager
Medsafe

Medicines Adverse Reactions Committee

Meeting date	**8 September 2016**	Agenda item	3.2.3
Title	**National immunisation schedule change to Gardasil 9 as a 2 dose schedule for boys and girls**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituents HPV 11 L1 protein HPV 16 L1 protein HPV 18 L1 protein HPV 31 L1 protein HPV 33 L1 protein HPV 45 L1 protein HPV 52 L1 protein HPV 58 L1 protein HPV 6 L1 protein	**Medicine** Gardasil 9	**Sponsors** MSD	
Funding	Funded		
Previous MARC meetings	The safety of Gardasil was discussed previously at the following meetings: – 163rd Meeting — 10 September 2015 Gardasil and autoimmune disease – 164th Meeting — 3 December 2015 Gardasil and complex regional pain syndrome, postural orthostatic tachycardia syndrome and other concerns		
International action	– The HPV vaccination programme is suspended in Japan, although the vaccine is still available for use. – EMA has reviewed the association between Gardasil and CRPS/POTS twice and concluded there is no link		
Prescriber Update	None		
Schedule	Prescription medicine		
Usage data	Estimated worldwide exposure for Gardasil at May 2016 was 72 million people. The estimated number of marketed 9vHPV vaccine doses distributed worldwide from market introduction to 30-Sep-2015 was approximately 3,997,235.		
Advice sought	**The Committee is asked to advise whether:** – The proposed monitoring and communication is adequate		

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1.0 PURPOSE

PHARMAC has recently announced changes to the National Immunisation Schedule. For human papillomavirus vaccine the following changes will take place from 1 January 2017.

- Funded access will be widened to include people up to the age of 26 years.
- A two-dose regimen will be funded for those children aged 14 years and under. The two-dose regimen was recently approved by Medsafe.
- A three-dose schedule will be funded for people aged 15-26 years inclusive.
- The 4 valent (Gardasil) HPV vaccine will be replaced with the 9 valent (Gardasil 9) vaccine.
- Females who have started a three-dose regimen of 4 valent Gardasil will be able to complete their remaining doses in 2017.

This is a significant change to the current programme which provides three doses of Gardasil and is given only to girls.

This paper presents information on the efficacy and safety of Gardasil 9. Information has been taken from the application for approval, the Risk Management Plan and the published scientific literature. The purpose of this paper is to review whether any additional actions are required from Medsafe in light of the changes to the immunisation schedule.

2.0 BACKGROUND

2.1 Human papilloma virus infection

HPV is the most common sexually transmitted infection worldwide. The cumulative lifetime risk for HPV infection in sexually active men and women exceeds 50%. The global prevalence of HPV infection is approximately 11-12%.

More than 202 different HPV types have been identified to date. Approximately 42 HPV types can infect the anogenital tract. [1]

Mucosal HPV types are divided into two groups:

- Low risk types cause genital warts, 6, 11, 40-44, 54, 61, 72 and 81
- High risk types cause cancer, 16, 18, 26, 31, 33, 39, 45, 51-53, 56, 58, 59, 66, 70, 73 and 82

The prevalence of HPV type differs between women with normal and abnormal cervical cytology.

Worldwide the most common HPV types detected in women with normal cervical cytology are 16, 18, 31/52, 51, 58, 56/39, 45 and 33. The HPV types most commonly detected in anogenital infections in women are similar to those in men.

Women in their late teens and early twenties are at highest risk for HPV infection.

Infections with multiple high-risk HPV types may increase the progression of premalignant cells to severe dysplasia (CIN1 to CIN3). Smokers have a higher risk of persistent HPV infection and a higher risk of developing HPV-associated cancers compared to non-smokers.

HPV infection and replication is entirely intraepithelial. The basal cell of the epithelium is the primary target of HPV infection. A minor lesion in the epithelium is sufficient to allow HPV to access this layer of cells. HPV binds to heparin sulfate proteoglycans of the basement membranes exposed after epithelial micro-trauma; then capsid protein L2 undergoes a conformational change that makes it susceptible to proteolysis, which in turn exposes a portion of capsid protein L1 that binds to an undetermined epithelial cell surface receptor. Because of this complex, multistep mechanism, the infection process is particularly slow, and transcription is not initiated before 12 to 24 hours.

Viral replication occurs only at a low level in the basal cells. High-level viral protein expression is achieved in the middle or upper layers of the epithelium. These layers of epithelial cells are normally terminally differentiated. However, with the up-regulation of viral proteins E6 and E7 that takes place during HPV infection, these cells are maintained in a mitotically active state that is conducive to viral DNA and protein synthesis. Viral assembly takes place only in terminally differentiated cells at the epithelium surface. Viral shedding occurs through the routine desquamation of dead epithelial cells.

Most HPV infections are asymptomatic and resolve spontaneously. 90% of HPV infections are cleared within 24 months. [1] In some cases, HPV infection is not cleared, resulting in persistent HPV infection. With time, persistent HPV infection produces elevated expression of the E6 and E7 viral proteins, viral deregulation, and progression toward high-grade dysplasia, which can lead to the development of cervical cancer, usually after 1 to 3 decades.

By remaining exclusively intraepithelial, HPV largely avoids exposure to the host immune system and largely evades immune recognition, which allows HPV infection to proceed.

Immune responses to natural viral infection are poor. In particular, low-level antibody responses to HPV become detectable only several months after the infection and in only approximately 50% of those infected. Nonetheless, most HPV infections are eventually cleared.

Several different conditions are caused, at least in part, by HPV infection.

2.1.1 Cervical cancer

The worldwide age-standardized incidence rate is 15.2 per 100,000 women. The rate in different populations are shown in table 1. Over 99% of cervical cancer is considered due to HPV infection.

Table 1 Age-standardised incidence rates of cervical cancer

Population	Number of Cancers	Rate per 100,000
World	530,232	15.2
Africa	80,419	25.2
Asia	312,990	15.3
Australia/New Zealand	798	5.0
Europe	54,517	10.6
European Union (EU-27)	31,038	9.0
Central and Eastern Europe	31,215	14.7
Northern Europe	5,213	8.4
Southern Europe	8,800	8.1
Western Europe	9,289	6.9
Latin America and Caribbean	68,220	23.5
South America	47,881	24.1
Northern America	12,491	5.7

The mortality rates for cervical cancer around the world are shown in table 2.
The number of cervical cancers registered in New Zealand in 2013 was 158; rate was 6.3 per 100,000. (New Zealand cancer data taken from the New Zealand Cancer Registry published on the Ministry of Health website see www.health.govt.nz/nz-health-statistics/national-collections-and-surveys/collections/new-zealand-cancer-registry-nzcr?mega=Health%20statistics&title=NZ%20Cancer%20Registry).

Table 2 Global age-standardised cervical cancer mortality rate

Population	Number of Deaths	Mortality Rate per 100,000
World	275,008	7.8
Africa	53,334	17.6
Asia	159,894	7.9
Australia/New Zealand	294	1.4
Europe	24,874	3.9
European Union (EU-27)	13,430	3.0
Central and Eastern Europe	15,437	6.2
Northern Europe	2,141	2.5
Southern Europe	3,49	2.5
Western Europe	3,837	2.0
Latin America and Caribbean	31,712	10.8
South America	21,836	10.8
Northern America	4,413	1.7

2.1.2 Vulvar cancer

Usual vulvar intraepithelial neoplasia (usual "VIN") has an HPV-related aetiology and is increasing worldwide (incidence rates approximately 5 per 100,000 women per year).

There were 56 registrations of vulvar cancer in New Zealand in 2013; 1.5 per 100,000.

2.1.3 Vaginal cancer

These carcinomas are rare (representing only 1 to 3% of gynaecological malignancies worldwide), occur mostly in older women (with 50% of the cases in women over the age of 70 years), and are primarily squamous cell carcinoma (approximately 80% of the cases).

There were 23 registrations of vaginal cancer in New Zealand in 2013; 0.7 per 100,000.

2.1.4 Anal cancer

HPV-related anal cancer is preceded by high-grade intraepithelial neoplasia (AIN), which has also been increasing in men and women over the past 30 years. Common risk factors among men and women are receptive anal sex, lifetime number of sexual partners, a history of genital warts, cigarette smoking, and immunosuppression (human immunodeficiency virus [HIV]-infected individuals, solid organ transplant recipients). Among women, additional risk factors are high-grade cervical or vulvar intraepithelial neoplasia. Age-standardized rates for anal cancer among men in Europe ranged from 0.2 (in Cyprus, Finland and Iceland) to 0.7 per 100,000 man-years (in the United Kingdom).

There were 32 registrations in men and 38 registrations in women of anal cancer in New Zealand in 2013. The rates were 1 and 1.2 per 100,000 in men and women respectively.

2.1.5 Penile cancer

Penile cancer is a relatively rare disease, representing less than 0.5% cancers in men.

There were 19 registrations of penile cancer in New Zealand in 2013; rate 0.6 per 100,000.

2.1.6 Oropharyngeal cancer

In the US in 2010, the overall rate for cancer of the oropharynx and tonsil was 2.3 per 100,000; with rates of 3.9 and 0.9 per 100,000 in males and females, respectively. The annual incidence of HPV-associated oropharyngeal cancer is now comparable to that of cervical cancer in the US. Oropharyngeal cancer affects both men and women, with a male:female ratio of approximately 4:1. Increasing trends of head and neck cancers at HPV associated sites have also been observed in Europe.

In New Zealand (2013) there were 16 registrations of oropharyngeal cancer (11 men, 5 women). There were 57 cancers of the tonsils (48 in men and 9 in women). The oropharyngeal cancer rates were 0.4 cases per 100,000 in men and 0.1 cases per 100,000 in women. The tonsil cancer rates were 1.6 and 0.3 per 100,000 in men and women respectively.

2.1.7 Anogenital warts

Reported annual incidence rates typically range between 1 and 2 new cases per 1,000 general adult population based on retrospective administrative databases, medical chart reviews and prospectively collected physician reports.

2.1.8 Recurrent Respiratory Papillomatosis

Pregnant women with HPV types 6 and 11—manifesting either subclinically or as genital warts—have a 50% to 70% risk of transferring the virus to the respiratory tract of the neonate during birth via the infected birth canal, which acts as a reservoir, and a 27.3% risk if delivery is via caesarean section, where the neonate may swallow infected amniotic fluid or maternal blood. Transmission of HPV types 6 or 11 may result in juvenile-onset recurrent respiratory papillomatosis, in which a child will develop benign airway-occluding respiratory papillomas requiring surgical removal. The annual incidence of this rare occurrence is 0.51 to 4 per 100,000 infants.[2]

Though the disease occurs at any age, it peaks in children between 2 to 4 years of age, and young adults between 20 to 40 years of age.

2.2 Gardasil 9 vaccine

Gardasil 9 vaccine is an aluminium adjuvanted recombinant protein particulate (virus-like particle [VLP]) vaccine. The 9vHPV vaccine contains the same HPV types already represented in the qHPV vaccine (HPV 6, 11, 16, and 18), as well as five additional HPV types (31, 33, 45, 52, and 58).

Based on epidemiology studies, the HPV types addressed by the 9v HPV vaccine (i.e., HPV 6/11/16/18/31/33/45/52/28) cause approximately:

- 90% of cervical cancers,
- more than 95% of adenocarcinoma in situ (AIS),
- 75-85% of high-grade cervical intraepithelial neoplasia (CIN 2/3),
- 85-90 % of HPV related vulvar cancers,
- 90-95 % of HPV related high-grade vulvar intraepithelial neoplasia (VIN 2/3),
- 80-85% of HPV related vaginal cancers,
- 75-85 % of HPV related high-grade vaginal intraepithelial neoplasia (VaIN 2/3),
- 90-95% of HPV related anal cancer,
- 85-90% of HPV related high-grade anal intraepithelial neoplasia (AIN2/3), and
- 90% of genital warts.

Each 0.5-mL dose of the vaccine contains approximately 500 mcg of aluminium (as amorphous aluminium hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate , residual traces of yeast protein (estimated at <0.7mcg/dose using a specific ELISA test) and water for injection. The product does not contain a preservative or antibiotics.

Since the prevalence of different HPV types varies between regions, Gardasil 9 is expected to protect against 86.5% of HPV-cervical cancer in New Zealand. This figure assumes 100% efficacy and the prevalence in New Zealand of different sub-types is the same as Australia.[1]

2.3 Data sheet

GARDASIL 9 is indicated in females aged 9 through 45 years for the prevention of cervical, vulvar, vaginal and anal cancer, precancerous or dysplastic lesions, genital warts, and infection caused by Human Papillomavirus (HPV) Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 (which are included in the vaccine).

GARDASIL 9 is indicated in males 9 through 26 years of age for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 (which are included in the vaccine).

The only contraindication is hypersensitivity to Gardasil or Gardasil 9.

Adverse effects are:

Table 3 Injection site and vaccine-related systemic adverse reactions reported at a frequency of ≥ 1%

Adverse Reaction	Women 16 Through 26 Years of Age GARDASIL 9 (N=8027) %	Girls and Boys 9 Through 15 Years of Age GARDASIL 9 (N=5280) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)		
Pain†	89.6	78.8
Swelling†	40.2	33.8
Erythema†	34.3	28.8
Pruritus	5.6	2.6
Bruising	1.7	0.0
Hematoma	1.3	2.0
Mass	1.2	0.2
Hemorrhage	0.9	1.0
Induration	0.7	1.7
Systemic Adverse Reactions (1 to 15 Days Postvaccination)		
Headache	14.7	12.7
Pyrexia	5.1	8.9
Nausea	4.2	2.2
Dizziness	2.9	1.6
Fatigue	2.3	1.3
Diarrhea	1.2	0.5
Oropharyngeal pain	1.0	0.8
Abdominal pain upper	0.7	1.3

*Data from Protocols 001, 002, 005, 006, 007, 009
†Designates a solicited adverse reaction
N=number of subjects vaccinated

Table 4 Injection site and vaccine-related systemic adverse reactions reported at a frequency of ≥ 1% for Gardasil 9 compared to Gardasil

Adverse Reaction	Women 16 Through 26 Years of Age		Girls 9 Through 15 Years of Age	
	GARDASIL 9 (N=7071) %	GARDASIL (N=7078) %	GARDASIL 9 (N=299) %	GARDASIL (N=300) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)				
Pain†	89.9	83.5	89.3	88.3
Swelling†	40.0	28.8	47.8	36.0
Erythema†	34.0	25.6	34.1	29.3
Pruritus	5.5	4.0	4.0	2.7
Bruising	1.9	1.9	‡	‡
Mass	1.3	0.6	‡	‡
Hemorrhage	1.0	0.7	1.0	2.0
Hematoma	0.9	0.6	3.7	4.7
Warmth	0.8	0.5	0.7	1.7
Induration	0.8	0.2	2.0	1.0
Reaction	0.6	0.6	0.3	1.0
Systemic Adverse Reactions (1 to 15 Days Postvaccination)				
Headache	14.6	13.7	11.4	11.3
Pyrexia	5.0	4.3	5.0	2.7
Nausea	4.4	3.7	3.0	3.7
Dizziness	3.0	2.8	0.7	0.7
Fatigue	2.3	2.1	0.0	2.7
Diarrhea	1.2	1.0	0.3	0.0
Myalgia	1.0	0.7	0.7	0.7
Oropharyngeal pain	1.0	0.6	2.7	0.7
Abdominal pain upper	0.7	0.8	1.7	1.3
Upper respiratory tract infection	0.1	0.1	0.3	1.0

*The data for women are from Protocol 001 and data for girls are from Protocol 009.
†Designates a solicited adverse reaction
‡There are no reports of injection-site bruising or mass for girls
N=number of subjects vaccinated

Post marketing reports:

- Infections and infestations: cellulitis
- Blood and lymphatic system disorders: idiopathic thrombocytopenic purpura, lymphadenopathy
- Nervous system disorders: acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, syncope sometimes accompanied by tonic-clonic movements.
- Gastrointestinal disorders: nausea, vomiting.
- Musculoskeletal and connective tissue disorders: arthralgia, myalgia
- General disorders and administration site conditions: asthenia, chills, fatigue, malaise.
- Immune system disorders: Hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria.

Medsafe comment
Most people experience an injection site reaction. More people experience injection site reactions with Gardasil 9 compared to Gardasil, this is not unexpected given the increased quantity of antigen and adjuvant.

3.0 SCIENTIFIC INFORMATION

Since Gardasil 9 contains the same antigen types as Gardasil it is relevant to first consider the efficacy and persistence of immune response for Gardasil.

3.1 Gardasil efficacy and safety

High efficacy was obtained with the quadrivalent vaccine in the FUTURE I and II trials (Table 5), associated with HPV16/18. The lower efficacy observed in the Intention To Treat (ITT) analysis, as compared to the IIT-naïve analysis, is explained by the inclusion of women with prevalent infection at entry. Neither Gardasil nor Gardasil 9 have therapeutic effects against HPV infection.

Irrespective of HPV type (ie, including types not in the vaccine), the efficacy (or effectiveness) was 43.0% (95% CI: 13.0–63.2) against CIN3 in the ITT-naïve and 16.4% in the ITT analysis.[3]

Table 5 protection of young women against incident cervical disease by Gardasil in the FUTURE I and II trials, for HPV 16 and 18.

	% Efficacy (95% CI)
ATP	
CIN2	100 (94.7–100)
CIN3	96.8 (88.1–99.6)
AIS	100 (30.9–100)
ITT-naïve	
CIN2	100 (91.9–100)
CIN3	100 (90.5–100)
AIS	100 (<0–100)
ITT	
CIN2	54.8 (40.8–65.7)
CIN3	45.1 (29.8–57.3)
AIS	60.0 (<0–87.3)

AIS: Adenocarcinoma in situ; ATP: According to Protocol; CI: Confidence interval; CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus; ITT: Intention-to-treat. Data from [30].

The Harding Center for Risk Literacy consider the effectiveness of Gardasil to be around 30% based on the FUTURE II study. They produce the fact box in figure 1.

Cervical Cancer Prevention

RISK LITERACY

with HPV vaccination (Gardasil). Numbers refer to women aged 12 to 25 years before their sexual debut. Numbers are shown per year.

Benefits of the vaccination when given in addition to the Pap-smear screening	100.000 without vaccination	100.000 with vaccination
How many women suffered from cervical cancer?	15	11
How many women died from cervical cancer?	3	2
Side effects		
How many women suffered from fever and sensitivity at the injection site?	-	1.000 - 10.000
How many women suffered from unspecific arthritis or hives?	-	10 - 1.000
How many women suffered from narrowed airways with serious shortness of breath?	-	1 - 10

Sources: Gesundheitsberichterstattung 2009 des Statistischen Bundesamtes. FUTURE II Study Group (2007) N Engl J Med 356. European Medicines Agency (2008) 31/10/2008 Gardasil H-C-703-II-13. Center for Disease Control and Prevention (CDC) (2008)

Figure 1 Fact box for Gardasil

In a meta-analysis, cross-protection was shown for the quadrivalent vaccine against HPV31.

Vaccination with HPV vaccines is expected to reduce the prevalence of the HPV vaccine types. There might, however, be concern how this would affect the distribution of other oncogenic HPV types. Human papillomaviruses are genetically very stable DNA viruses. Escape mutants or new HPV types are therefore unlikely to develop. But even if type replacement would occur, it remains to be seen if it would have implications on public health. The risk of developing cancer due to HPV16 or 18 is much higher than the risk of developing cancer by other HPV types. [3] Studies investigating the effect of Gardasil have not shown any replacement effects to date.

The safety of Gardasil vaccination in boys has also been studied in Australia when the immunisation programme changed to include boys. A summary of the observational study was published on the TGA website (https://www.tga.gov.au/alert/gardasil-quadrivalent-human-papillomavirus-vaccine-update-2). No safety concerns were identified.

3.1.1 Persistence of immune responses to Gardasil [4]

The qHPV (HPV6, 11, 16, and 18) vaccine long-term follow-up (LTFU) study is an ongoing extension of the pivotal clinical study (FUTURE II) taking place in the Nordic region.

The LTFU study was designed to evaluate the effectiveness, immunogenicity, and safety of the qHPV vaccine (Gardasil) for at least 10 years following completion of the base study. The most recent report presented immunogenicity data from testing samples of the year 5 LTFU visit (approximately 9 years after vaccination).

FUTURE II vaccination arm subjects, who consented to being followed in the LTFU, donated serum at regular intervals. Anti-HPV6, -11, -16, and -18 antibodies were detected by the competitive Luminex immunoassay (cLIA), and in addition, serum samples from 2012 were analysed by the total IgG Luminex immunoassay (LIA) (n= 1,598). cLIA geometric mean titres (GMTs) remained between 70% and 93% of their month 48 value depending on HPV type. For all HPV types, the lower bound of the 95% confidence interval (CI) for the year 9 GMTs remained above the serostatus cutoff value.

Table 6 Summary of anti-HPV cLIA GMTs in the per-protocol immunogenicity population

Antibody type	Time point[a] (mo)	No. of subjects	GMT (mMU/ml)	95% CI (mMU/ml)
Anti-HPV6	7	237	517.6	466.0, 574.9
	24	246	131.2	116.4, 148.0
	48	1,121	96.5	91.2, 102.2
	108	1,233	89.3	84.8, 94.0
Anti-HPV11	7	238	736.3	656.2, 826.0
	24	246	170.9	152.6, 191.5
	48	1,121	121.6	115.1, 128.4
	108	1,233	85.2	80.7, 90.0
Anti-HPV16	7	228	2,213.0	1,871.6, 2,616.8
	24	237	532.2	468.6, 604.5
	48	1,206	485.0	455.3, 516.6
	108	1,178	348.3	328.0, 369.9
Anti-HPV18	7	259	420.9	368.6, 480.6
	24	269	57.2	48.3, 67.8
	48	1,206	43.3	39.9, 47.1
	108	1,331	32.5	30.3, 34.9

[a] Month 48 visits were generally scheduled earlier than month 48. This time point includes all visits occurring within 6 months of the approximate mean interval of 44 months. Month 108 visits were generally scheduled approximately 9 years after the first dose of qHPV vaccine. This time point also corresponds to 5 years after the start of the LTFU study.

The seropositivity cutoffs of the HPV cLIA were assessed using a panel of serum samples from subjects highly likely to be HPV-naive (children) and from subjects who were highly likely to be HPV

seropositive. Any sample with a value less than the cutoff was considered serostatus negative. Samples with values equal to or greater than the cutoff were considered serostatus positive. Serostatus cutoff values for HPV6, -11, -16, and -18 were 20 mMU/ml, 16 mMU/ml, 20 mMU/ml, and 24 mMU/ml, respectively.

The proportion of subjects who remained seropositive based on the IgG LIA was higher than the proportion based on cLIA, especially for anti-HPV18. As expected, the anti-HPV serum IgG and cLIA responses were strongly correlated for all HPV types.

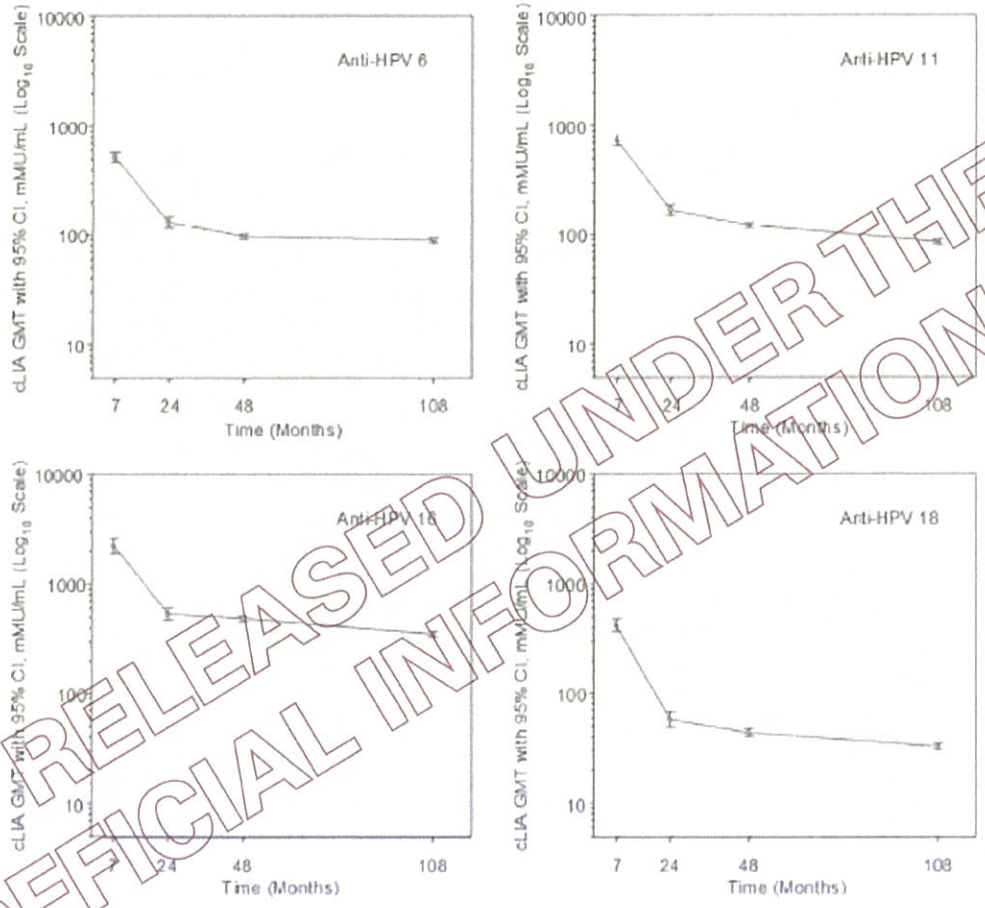


Figure 2 Longitudinal anti-HPV6, -11, -16 and -18 cLIA GMTs. The y axis is a log scale

The authors are running a concomitant clinical study investigating clinical outcomes which has 8 years of follow-up. Despite the observed decrease in anti-HPV18 GMTs no HPV18-related breakthrough cases have been detected, which underlines that the drop of anti-HPV18 GMTs as measured by cLIA is most likely not predictive for vaccine effectiveness.

The critical level of anti-HPV antibodies representing an immunological correlate for vaccine effectiveness remains to be assessed. It is possible that the drop in anti-HPV18 GMTs is a function of the assay rather than reflecting lower immunogenicity.

The authors concluded Anti- HPV GMTs and the proportion of vaccinated individuals who are seropositive remain high for up to 9 years of follow-up after vaccination.[4]

Medsafe comments

The concomitant clinical study has only been published as a conference abstract. The plateau in figure 2 for all vaccines types suggests that protection will be long-lived. The estimated seropositive level is likely conservative given the clinical results and antibody studies in 'natural' infection showing

clearance of HPV without detectable antibody levels. Overall the available data suggest a long-lasting protective effect.

3.1.2 Sexual activity

Since the inception of the HPV vaccine, there have been parental concerns that providing a vaccine to prevent a sexually transmitted infection may encourage children and adolescents to engage in sexual activity. A number of studies have been conducted investigating this topic.

A cohort of 1398 11- and 12-year-old girls was followed over a period of 3 years; 1 group was vaccinated against HPV and the other was not. The results showed virtually no difference between the 2 groups over that time period, with 2 girls in each group becoming pregnant and 1 vaccinated and 3 non-vaccinated girls receiving diagnoses of infection with chlamydia.[2]

Forster et al [5] examined whether HPV vaccination influences sexual behaviour in adolescent girls through cross-sectional and longitudinal surveys in 7 English schools. Selection of schools was opportunistic, but the authors deliberately included some locations known to be deprived and ethnically diverse. In four of the schools, over 50% of students were from ethnic minority backgrounds and over 50% were receiving educational maintenance allowance (EMA2). Four schools offered school-based vaccination and in the other three, girls had to visit their GP or local pharmacist to receive the vaccine.

The cross-sectional survey included 1053 girls (mean age 17.1 years) who had (n = 433 recruited in March 2010) or had not (n = 620 recruited in March 2009) been offered the HPV vaccine. The longitudinal survey included 407 girls (mean age 17.5 years) who had been offered HPV vaccination and had either received at least one dose (n = 148) or had not received any doses (n = 259).

The authors used chi-square tests and an independent t-test to examine demographic differences between the vaccinated and unvaccinated groups. A zero-inflated Poisson regression adjusting for clustering by school was used to compare change in number of sexual partners in the vaccinated and unvaccinated group as a high proportion of the sample had zero sexual partners.

Table 7 Demographic characteristics of the samples

	Cross-sectional survey			Longitudinal survey		
	Total, *n* (%) (*n* = 1053)	Offered vaccine (surveyed March 2010), *n* (%) (*n* = 433)	Not offered vaccine (surveyed March 2009), *n* (%) (*n* = 620)	Total, *n* (%) (*n* = 407)	Vaccinated at follow-up, *n* (%) (*n* = 148)	Un-vaccinated at follow-up, *n* (%) (*n* = 259)
Ethnicity						
White	633 (61.7)	293 (68.8)	340 (56.8)	246 (63.2)	98 (69.5)	148 (59.7)
Black	113 (13.0)	34 (8.0)	79 (13.2)	31 (8.0)	5 (3.5)	26 (10.5)
Asian	168 (16.4)	54 (12.7)	114 (19.0)	73 (18.8)	28 (19.9)	45 (18.1)
Other	111 (10.9)	45 (10.6)	66 (11.0)	39 (10.0)	10 (7.1)	29 (11.7)
EMA receipt						
£30	355 (34.7)	137 (32.2)	218 (36.5)	138 (35.4)	54 (38.0)	84 (33.9)
£20	44 (4.3)	16 (3.8)	28 (4.7)	15 (3.8)	7 (4.9)	8 (3.2)
£10	46 (4.5)	15 (3.5)	31 (5.2)	14 (3.6)	4 (2.8)	10 (4.0)
None	578 (56.5)	257 (60.5)	321 (53.7)	223 (57.2)	77 (54.2)	146 (58.9)
Religion						
None	373 (36.2)	172 (40.7)	201 (33.2)	136 (34.9)	53 (37.9)	83 (33.2)
Christian	431 (41.9)	180 (42.6)	251 (41.5)	159 (40.8)	48 (34.3)	111 (44.4)
Muslim	134 (13.0)	51 (12.1)	83 (13.7)	68 (17.4)	27 (19.3)	41 (16.4)
Other	91 (8.84)	20 (5.0)	71 (11.7)	27 (6.8)	12 (8.6)	15 (6.0)
Age (mean (se))	17.1 (0.07)	17.1 (0.02)	17.0 (0.20)	17.51 (0.02)	17.5 (0.1)	17.5 (< 01)

Note: Total columns not equalling the total for the sample are due to missing data.
* Significant difference of $p < 0.05$ between the two groups.

In the cross-sectional survey, the group of girls who had been offered the HPV vaccine were no more likely to be sexually active than the group of girls who had not been offered the HPV vaccine.

In the longitudinal survey, the vaccinated group were no more likely to have changed their condom use or increased their total number of sexual partners than the unvaccinated group.

Table 8 Between-group differences in changes in sexual behaviour from baseline to follow up

Vaccination status	Baseline (September 2009)	Follow-up (March 2010)	Change score	*p*	
Reported number of sexual partners (*n* = 405) mean (se)					
Vaccinated	0.83 (0.18)	1.14 (0.15)	0.31	0.38[a]	–
Unvaccinated	0.65 (0.24)	0.90 (0.33)	0.25		–
Vaccination status	**Baseline (September 2009)**	**Follow-up (March 2010)**	**Percentage change**	***p***	**OR (CI)**
Respondents reporting having reached sexual debut (*n* = 395), *n* (%)					
Vaccinated	57 (39.3)	69 (47.6)	8.3	0.44[b]	Reference
Unvaccinated	90 (36.0)	105 (42.0)	6.0		0.80 (0.04–1.59)
Respondents reporting inconsistent condom use (*n* = 135), *n* (%)					
Vaccinated	33 (64.7)	36 (70.6)	5.9	0.45[c]	Reference
Unvaccinated	53 (63.1)	55 (65.5)	2.4		0.88 (0.58–1.33)

Note: n in headings is n used in analyses. Numbers vary due to missing data.

[a] Difference in follow-up score, adjusting for girls' subjective norms for having sex, their drug use, and whether they had ever had a boyfriend.

[b] Difference in proportion reporting having ever had sex at follow-up, adjusting the baseline proportions.

[c] Difference in proportion reporting inconsistent condom use at follow-up, adjusting the baseline proportions (analysis only includes girls who were sexually active at baseline).

The authors concluded that neither being offered the HPV vaccine nor receiving it affected sexual behaviour.

Medsafe comments

Multiple studies have investigated sexual behaviour, no changes in practices have been detected.

3.2 Overall clinical trial exposure for Gardasil 9

The exposure by dose is shown in table 9 and by age in table 10

Table 9 Exposure to 9vHPV in clinical trials by dose

	9vHPV in the 3 dose schedule		9vHPV in the 2 dose schedules	
Dose	Randomised blinded trials	Integrated clinical trials	0,6 regimen	0,12 regimen
Vaccination 1	8005	15875	602	300
Vaccination 2	7908	15631	589	291
Vaccination 3	7812	15427		

Table 10 Exposure to 9vHPV in clinical trials by age and gender

Age (years)	9vHPV in the 3 dose schedule				9vHPV in the 2 dose schedules			
	Randomised blinded trials		Integrated clinical trials		0, 6 regimen		0, 12 regimen	
	male	female	male	female	male	female	Male	female
<9	0	0	0	0	0	0	0	0
9-15	0	420	811	501	301	301	150	151
16-17	0	263	187	417	0	0	0	0
18-26	0	7322	1225	8728	0	0	0	0
>26	0	0	2	4	0	0	0	0

3.3 Efficacy and effectiveness of Gardasil 9

The initial application for approval contained the following data.

- Pivotal study 001: Non-inferior immunogenicity (4 original types) of 9vHPV in females (16 to 26 yrs) versus qHPV in 16 to 26 yrs
- Immunological Bridging (002 and 009)
- Prior exposure to Gardasil (006)
- Supporting Studies: concomitant use with other vaccines (005 and 007).

Following the initial application the company applied for a two dose schedule.

The majority of the initial clinical studies have now been published in the literature; in this report the data available in the literature is presented where possible.

In the majority of clinical studies the comparator was Gardasil since it was considered unethical to use placebo. The criteria used for non-inferiority, seroconversion and the data analyses were consistent throughout these studies.

3.3.1 Protocol V503-001 Efficacy of Gardasil 9 versus Gardasil.[6]

Study 001 study was designed as a combination of 3 sub-studies (figure 3):

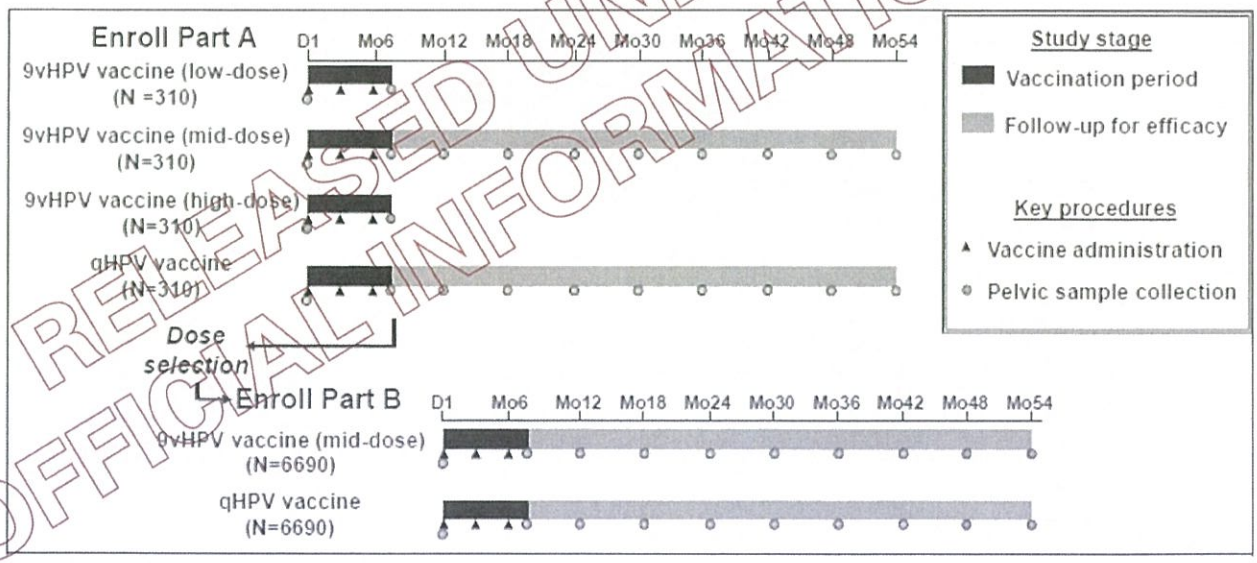


Figure 3 Overview of study design

1. A Phase IIb dose-ranging sub-study including all subjects enrolled under Part A, to select a vaccine dose formulation for the 9vHPV vaccine program based on immunogenicity and safety assessment through Month 7.

Women, 16 to 26 years of age, were randomized in equal numbers to 1 of 3 dose formulations of the 9vHPV vaccine or the comparator qHPV vaccine, in a 3-dose regimen.

The dose selected for the second part of Study 001 was the mid-dose.

The mid-dose formulation contains increased amounts of HPV 6, 16, and 18 VLPs than the qHPV vaccine and has an adjuvant-to-antigen ratio that is similar to that of the qHPV vaccine.

This dose was then used in all subsequent studies.

2. A Phase III efficacy sub-study including those subjects enrolled under Part A who received the selected dose formulation of 9vHPV vaccine (mid-dose 9vHPV vaccine) or the qHPV vaccine control,

and additional subjects enrolled under Part B, to assess the efficacy and safety objectives of the study.

The additional healthy 16- to 26-year-old women were randomized in equal numbers to the selected 9vHPV vaccine dose formulation chosen from Part A or the comparator qHPV vaccine.

Pelvic samples, including external genital and cervicovaginal swabs and Pap test samples, were collected at Day 1, Month 7, Month 12, Month 18, Month 24, Month 30, Month 36, Month 42, Month 48, and Month 54.

3. A Phase III immunogenicity sub-study, that included subjects enrolled under Part B, to assess the immunogenicity objectives of the study.

A 3-dose regimen (0, 2 and 6 months) was followed-up for safety and efficacy for 54 months. Immunogenicity was assessed at Month 7, followed by assessment of persistence of antibody responses through Month 42.

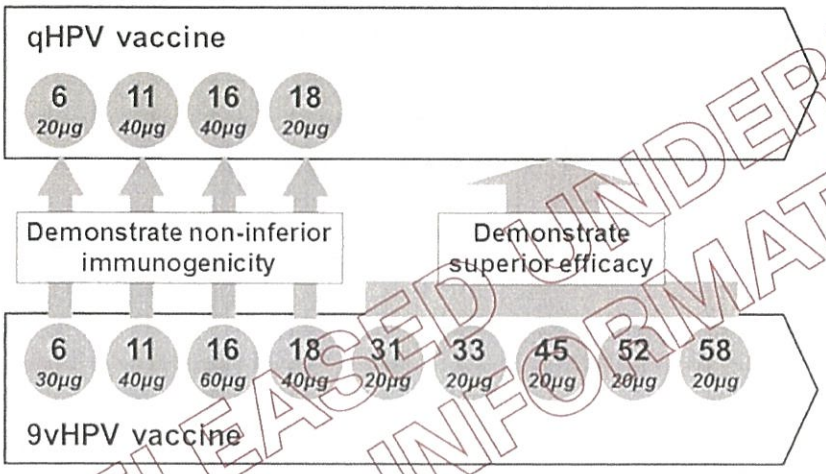


Figure 4 Primary efficacy objectives of protocol V503-001

Neutralizing antibodies are recognized as the vaccine-induced immune mechanism of protection against HPV infection and disease. Since no immune threshold of protection has been identified for HPV vaccines, immunogenicity of the 9vHPV vaccine was compared to that of the qHPV vaccine.

Approximately 14,000 females 16 to 26 years of age were randomised to Gardasil 9 or quadrivalent Gardasil. The study sites were located in 6 countries in the Asia-Pacific region (Hong Kong, Japan, New Zealand, Republic of Korea, Taiwan, and Thailand), 5 countries in Europe (Austria, Denmark, Germany, Norway, and Sweden), 5 countries in Latin America (Brazil, Chile, Colombia, Mexico, and Peru) and 2 countries in North America (Canada and the United States, including US Territory Puerto Rico). Study dates were September 2007 to April 2013.

Table 11 Baseline characteristics of the participants

Characteristic	9vHPV Vaccine (N=7106)	qHPV Vaccine (N=7109)	Total (N=14,215)
Age — yr			
Mean	21.9±2.5	21.8±2.5	21.9±2.5
Median	22.0	22.0	22.0
Range	16–26	16–26	16–26
Age at first sexual intercourse — yr	17.4±2.2	17.4±2.2	17.4±2.2
Region — no. (%)			
Asia–Pacific	905 (12.7)	909 (12.8)	1,814 (12.8)
Europe	2406 (33.9)	2409 (33.9)	4,815 (33.9)
Latin America	2372 (33.4)	2372 (33.4)	4,744 (33.4)
North America	1423 (20.0)	1419 (20.0)	2,842 (20.0)
Smoking status — no. (%)			
Current smoker	1071 (15.1)	1005 (14.1)	2,076 (14.6)
Former smoker	382 (5.4)	358 (5.0)	740 (5.2)
Never smoked	5647 (79.5)	5744 (80.8)	11,391 (80.1)
Unknown	6 (0.1)	2 (0)	8 (0.1)
Lifetime sexual partners — no. (%)†			
1	2063 (29.0)	2023 (28.5)	4,086 (28.8)
2	1691 (23.8)	1698 (23.9)	3,389 (23.8)
3	1648 (23.2)	1646 (23.2)	3,294 (23.2)
4	1520 (21.4)	1527 (21.5)	3,047 (21.4)
>4	11 (0.2)	15 (0.2)	26 (0.2)
Non-HPV–related cervicovaginal infections or sexually transmitted diseases			
Any	298 (4.2)	292 (4.1)	590 (4.2)
Chlamydia	284 (4.0)	285 (4.0)	569 (4.0)
Gonorrhea	19 (0.3)	11 (0.2)	30 (0.2)
Contraceptive use‡			
Barrier	2318 (32.6)	2303 (32.4)	4,621 (32.5)
Behavior	1014 (14.3)	1035 (14.6)	2,049 (14.4)
Hormonal	4273 (60.2)	4292 (60.4)	8,565 (60.3)
Day 1 composite HPV positivity — no./total no. (%)§			
Serologic test	2771/7082 (39.1)	2647/7078 (37.4)	5418/14,160 (38.3)
PCR assay	1887/6919 (27.3)	1920/6943 (27.7)	3807/13,862 (27.5)
Serologic test or PCR assay	3365/6970 (48.3)	3345/6983 (47.9)	6710/13,953 (48.1)

* Plus–minus values are means ±SD. The baseline characteristics of the two study groups were similar. The quadrivalent human papillomavirus (HPV) vaccine (qHPV) targets HPV types 6, 11, 16, and 18; the 9-valent viruslike particle vaccine (9vHPV) targets the HPV types in the qHPV vaccine and five additional oncogenic types (31, 33, 45, 52, and 58). PCR denotes polymerase chain reaction.

† The percentages for the number of lifetime sexual partners were calculated on the basis of the number of participants for whom there were data on sexual history at enrollment (7102 in the 9vHPV group and 7108 in the qHPV group).

‡ Participants may have used more than one contraceptive method. A participant is counted once within a category and may be counted in more than one category. The percentages for the numbers of participants who used contraceptives were based on the number for whom this information was available (7102 in the 9vHPV group and 7104 in the qHPV group).

§ Positivity was defined as an anti-HPV titer on immunoassay of at least 30, 16, 20, 24, 10, 8, 8, 8, and 8 for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively. The numerator in this category represents the number of HPV-positive participants, and the denominator the total number of participants with assay results that could be evaluated.

Results in the PPE (per-protocol efficacy) Population

All subjects in the PPE population were required to be seronegative to the relevant HPV type at Day 1 and PCR-negative to the relevant HPV type from Day 1 through Month 7, have received all 3 vaccinations within protocol-specified visit windows, and have no protocol violation.

Table 12 Efficacy against CIN2/3, AIS, Cervical cancer, VIN2/3, VaIN2/3, vulvar cancer and vaginal cancer

End Point	9vHPV Vaccine (N=7099)		qHPV Vaccine (N=7105)		Risk Reduction (95% CI)
	no./total no.	*cases/1000 person-yr*	*no./total no.*	*cases/1000 person-yr*	
Modified intention-to-treat population					
High-grade cervical, vulvar, and vaginal disease†					
All participants	340/7027	14.0	344/7027	14.0	0.7 (-15.7 to 14.8)
HPV-uninfected on day 1	26/3032	2.4	46/3077	4.2	42.5 (7.9 to 65.9)
Not related to 9 vaccine HPV types‡	26/3032	2.4	33/3077	3.0	19.7 (-34.5 to 52.5)
Related to 9 vaccine HPV types‡	0/3032	0.0	13/3076	1.2	100 (70.4 to 100)
HPV-infected on day 1	314/3995	23.1	298/3850	22.1	-4.8 (-23.3 to 10.8)
Not related to 9 vaccine HPV types‡	141/3995	10.0	137/3950	9.8	-2.0 (-30.9 to 19.8)
Related to 9 vaccine HPV types‡	173/3992	12.4	161/3946	11.6	-6.8 (-33.2 to 14.3)
Average risk reduction§	—	—	—	—	19.0 (-1.6 to 35.3)
High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer					
All participants	325/6882	14.1	326/6871	14.1	-0.3 (-17.3 to 14.3)
HPV-uninfected on day 1	26/2976	2.5	44/3009	4.2	39.7 (1.8 to 64.3)
Not related to 9 vaccine HPV types‡	26/2976	2.5	31/3009	3.0	14.3 (-49.1 to 49.1)
Related to 9 vaccine HPV types‡	0/2976	0.0	13/3009	1.2	100 (70.3 to 100)
HPV-infected on day 1	299/3906	23.3	282/3862	22.2	-5.3 (-24.1 to 10.8)
Not related to 9 vaccine HPV types‡	131/3906	10.1	132/3862	10.3	1.8 (-26.0 to 23.5)
Related to 9 vaccine HPV types‡	168/3906	13.0	150/3862	11.7	-11.3 (-39.6 to 11.0)
Average risk reduction§	—	—	—	—	17.1 (-4.2 to 34.0)
Per-protocol efficacy population					
High-grade cervical, vulvar, and vaginal disease¶					
Related to HPV-31, 33, 45, 52, or 58	1/6016	0.1	30/6,017	1.6	96.7 (80.9 to 99.8)
Related to HPV-6, 11, 16, or 18	1/5883	0.1	3/5898	0.2	66.6 (-203.0 to 98.7)
High-grade cervical epithelial neoplasia, adenocarcinoma in situ, and cervical cancer					
Related to HPV-31, 33, 45, 52, or 58	1/5948	0.1	27/5943	1.5	96.3 (79.5 to 99.8)
Related to HPV-6, 11, 16, or 18	1/5823	0.1	1/5832	0.1	-0.4 (≤ -999 to 97.4)
Persistent infection ≥6 months' duration¶					
Related to HPV-31, 33, 45, 52, or 58	35/5939	2.1	810/5953	52.4	96.0 (94.4 to 97.2)
Related to HPV-6, 11, 16, or 18	59/5812	3.6	80/5830	5.0	26.4 (-4.3 to 47.5)

* The total number of participants (N) includes those who received at least one dose of a study vaccine; the no./total no. refers to the number of participants with an end point among the participants who received at least one dose of a study vaccine and had at least one follow-up visit. The modified intention-to-treat population consisted of participants who received at least one dose of vaccine and for whom there was at least one measurement of efficacy for the end point being analyzed. The per-protocol efficacy population consisted of participants who received all three doses of vaccine within 1 year, were HPV-uninfected (i.e., were seronegative at day 1 and had negative results on PCR assays for all HPV types tested from day 1 through month 7) to the vaccine HPV type being analyzed, and had no protocol violations. CI denotes confidence interval.

† This category includes high-grade cervical epithelial neoplasia, adenocarcinoma in situ, cervical cancer, high-grade vulvar intraepithelial neoplasia, high-grade vaginal intraepithelial neoplasia, vulvar cancer, and vaginal cancer.

‡ The nine vaccine HPV types are 6, 11, 16, 18, 31, 33, 45, 52, and 58. Participants with end-point conditions related to the nine vaccine HPV types were those who at any time during the study received a diagnosis of the indicated disease related to any of the nine HPV types included in the vaccine and, in addition, did not receive a diagnosis of the indicated disease at any time during the study that was not related to one of the nine HPV types included in the vaccine. Participants with end-point conditions were counted only once and in only one of these two categories. The sum of case counts in these two categories is equal to the number of end-point cases irrespective of HPV type.

§ The risk reduction shown represents the sample-size–weighted average of the risk reduction in the HPV-uninfected and the HPV-infected subgroups. The HPV-uninfected subgroup consisted of participants who had the following characteristics on day 1: a negative finding for squamous intraepithelial lesions, a seronegative finding for the nine vaccine-HPV types, and negative results on PCR assays for all HPV types tested during the study (types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59). The HPV-infected subgroup consisted of all participants who were not in the HPV-infected subgroup.

¶ Persistent infection was defined as detection of the same HPV type in a genital swab or tissue specimen collected on two or more consecutive visits, with an interval of at least 6 months (±1 month) between the visits.

Table 13 Analysis of efficacy against infection and disease in the mITT and PPE populations

	9vHPV Vaccine (N=7,099)			qHPV Vaccine (N=7,105)			
	Evaluable Subjects	No. of Cases	Rate[†]	Evaluable Subjects	No. of Cases	Rate[†]	Vaccine Efficacy % (95% CI)
Per-Protocol Efficacy Population (PPE)							
HPV 31/33/45/52/58-related endpoints							
Persistent infection ≥6 months	5,939	35	2.1	5,953	810	52.4	96.0 (94.4, 97.2)
Persistent infection ≥12 months	5,939	21	1.3	5,953	544	34.5	96.3 (94.4, 97.7)
Cervical, vulvar, and vaginal disease[‡]	6,016	3	0.2	6,017	103	5.5	97.1 (91.8, 99.2)
Low-grade disease[§]	6,016	2	0.1	6,017	82	4.3	97.6 (91.7, 99.6)
High-grade disease[¶]	6,016	1	0.1	6,017	30	1.6	96.7 (80.9, 99.8)
Cervical disease[‡]	5,948	2	0.1	5,943	88	5.1	97.7 (92.2, 99.6)
CIN 1	5,948	1	0.1	5,943	69	4.0	98.6 (92.4, 99.9)
CIN 2/3 or worse	5,948	1	0.1	5,943	27	1.5	96.3 (79.5, 99.8)
Vulvar and vaginal disease[‡]	6,009	1	0.1	6,012	16	0.8	93.8 (61.5, 99.7)
Condyloma	6,009	0	0.0	6,012	3	0.2	100 (-71.6, 100)
VIN 1 or VaIN 1	6,009	1	0.1	6,012	12	0.6	91.7 (51.3, 99.6)
VIN 2/3 or VaIN 2/3 or worse	6,009	0	0.0	6,012	3	0.2	100 (-71.5, 100)
HPV 31-related endpoints							
Persistent infection ≥6 months	5,251	7	0.5	5,198	150	10.5	95.5 (90.7, 97.9)
Persistent infection ≥12 months	5,251	4	0.3	5,198	97	6.7	96.0 (89.9, 98.6)
Cervical, vulvar, and vaginal disease[‡]	5,308	1	0.1	5,252	18	1.1	94.5 (68.0, 99.7)
Low-grade disease[§]	5,308	1	0.1	5,252	15	0.9	93.4 (57.9, 99.7)
High-grade disease[¶]	5,308	0	0.0	5,252	7	0.4	100 (40.1, 100)
Cervical disease[‡]	5,259	1	0.1	5,200	16	1.0	93.8 (61.9, 99.7)
CIN 1	5,259	1	0.1	5,200	13	0.9	92.4 (55.1, 99.6)
CIN 2/3 or worse	5,259	0	0.0	5,200	7	0.5	100 (40.1, 100)
Vulvar and vaginal disease[‡]	5,304	0	0.0	5,247	3	0.2	100 (-69.7, 100)
Condyloma	5,304	0	0.0	5,247	0	0.0	NA
VIN 1 or VaIN 1	5,304	0	0.0	5,247	3	0.2	100 (-69.7, 100)
VIN 2/3 or VaIN 2/3 or worse	5,304	0	0.0	5,247	0	0.0	NA
HPV 33-related endpoints							
Persistent infection ≥6 months	5,553	1	0.1	5,560	106	6.9	99.1 (95.2, 100)
Persistent infection ≥12 months	5,553	1	0.1	5,560	79	5.1	98.7 (93.5, 99.9)
Cervical, vulvar, and vaginal disease[‡]	5,624	0	0.0	5,628	16	0.9	100 (75.4, 100)
Low-grade disease[§]	5,624	0	0.0	5,628	11	0.6	100 (66.7, 100)
High-grade disease[¶]	5,624	0	0.0	5,628	7	0.4	100 (39.3, 100)
Cervical disease[‡]	5,565	0	0.0	5,563	14	0.9	100 (70.0, 100)
CIN 1	5,565	0	0.0	5,563	9	0.5	100 (57.1, 100)
CIN 2/3 or worse	5,565	0	0.0	5,563	6	0.4	100 (32.5, 100)
Vulvar and vaginal disease[‡]	5,617	0	0.0	5,624	2	0.1	100 (-248.2, 100)
Condyloma	5,617	0	0.0	5,624	0	0.0	NA
VIN 1 or VaIN 1	5,617	0	0.0	5,624	2	0.1	100 (-248.2, 100)
VIN 2/3 or VaIN 2/3 or worse	5,617	0	0.0	5,624	1	0.1	100 (≤ -999, 100)

	9vHPV Vaccine (N=7,099)			qHPV Vaccine (N=7,105)			
	Evaluable Subjects	No. of Cases	Rate*	Evaluable Subjects	No. of Cases	Rate*	Vaccine Efficacy % (95% CI)
HPV 45-related endpoints							
Persistent infection ≥6 months	5,649	4	0.3	5,658	124	7.9	96.8 (92.1, 98.9)
Persistent infection ≥12 months	5,649	2	0.1	5,658	73	4.7	97.3 (90.7, 99.5)
Cervical, vulvar, and vaginal disease†	5,724	0	0.0	5,724	8	0.4	100 (46.5, 100)
Low-grade disease‡	5,724	0	0.0	5,724	6	0.3	100 (32.9, 100)
High-grade disease¶	5,724	0	0.0	5,724	2	0.1	100 (-246.8, 100)
Cervical disease†	5,658	0	0.0	5,659	6	0.4	100 (32.7, 100)
CIN 1	5,658	0	0.0	5,659	4	0.2	100 (-11.7, 100)
CIN 2/3 or worse	5,658	0	0.0	5,659	2	0.1	100 (-247.7, 100)
Vulvar and vaginal disease†	5,718	0	0.0	5,719	2	0.1	100 (-246.9, 100)
Condyloma	5,718	0	0.0	5,719	0	0.0	NA
VIN 1 or VaIN 1	5,718	0	0.0	5,719	2	0.1	100 (-246.9, 100)
VIN 2/3 or VaIN 2/3 or worse	5,718	0	0.0	5,719	0	0.0	NA
HPV 52-related endpoints							
Persistent infection ≥6 months	5,263	11	0.7	5,160	387	27.9	97.3 (89.3, 98.7)
Persistent infection ≥12 months	5,263	7	0.5	5,160	238	16.9	97.2 (94.2, 98.7)
Cervical, vulvar, and vaginal disease†	5,320	1	0.1	5,216	46	3.8	97.9 (88.3, 99.9)
Low-grade disease‡	5,320	1	0.1	5,216	38	2.3	97.4 (85.3, 99.9)
High-grade disease¶	5,320	0	0.0	5,216	11	0.7	100 (67.3, 100)
Cervical disease†	5,274	0	0.0	5,159	37	2.4	100 (91.1, 100)
CIN 1	5,274	0	0.0	5,159	29	1.9	100 (88.7, 100)
CIN 2/3 or worse	5,274	0	0.0	5,159	11	0.7	100 (67.4, 100)
Vulvar and vaginal disease†	5,314	1	0.1	5,212	9	0.5	89.1 (21.6, 99.5)
Condyloma	5,314	0	0.0	5,212	3	0.2	100 (-68.6, 100)
VIN 1 or VaIN 1	5,314	1	0.1	5,212	7	0.4	86.0 (1.7, 99.4)
VIN 2/3 or VaIN 2/3 or worse	5,314	0	0.0	5,212	0	0.0	NA
HPV 58-related endpoints							
Persistent infection ≥6 months	5,297	12	0.8	5,284	225	15.6	94.8 (91.0, 97.1)
Persistent infection ≥12 months	5,297	7	0.5	5,284	145	10.0	95.3 (90.4, 97.8)
Cervical, vulvar, and vaginal disease†	5,361	1	0.1	5,340	26	1.5	96.2 (78.9, 99.8)
Low-grade disease‡	5,361	0	0.0	5,340	21	1.2	100 (83.0, 100)
High-grade disease¶	5,361	1	0.1	5,340	6	0.4	83.4 (-23.9, 99.3)
Cervical disease†	5,307	1	0.1	5,284	23	1.5	95.7 (76.4, 99.8)
CIN 1	5,307	0	0.0	5,284	20	1.3	100 (81.9, 100)
CIN 2/3 or worse	5,307	1	0.1	5,284	4	0.3	75.1 (-91.4, 99.0)
Vulvar and vaginal disease†	5,356	0	0.0	5,335	3	0.2	100 (-70.9, 100)
Condyloma	5,356	0	0.0	5,335	0	0.0	NA
VIN 1 or VaIN 1	5,356	0	0.0	5,335	1	0.1	100 (≤ -999, 100)
VIN 2/3 or VaIN 2/3 or worse	5,356	0	0.0	5,335	2	0.1	100 (-246.2, 100)
Modified Intention-to-Treat Population (mITT)							
HPV 31/33/45/52/58-related endpoints							

Persistent infection ≥6 months[†]	6,818	795	38.9	6,822	1,759	93.4	80.2 (76.3, 83.4)
Mostly HPV Naive	2,965	26	2.6	3,002	443	47.7	94.5 (91.8, 96.3)
Not HPV Naive	3,853	769	72.4	3,820	1,316	137.9	47.5 (42.6, 52.0)
Persistent infection ≥12 months[†]	6,799	613	29.4	6,818	1,297	65.9	79.1 (74.2, 83.0)
Mostly HPV Naive	2,965	19	1.9	3,002	321	33.9	94.3 (91.0, 96.6)
Not HPV Naive	3,834	594	54.1	3,816	976	95.5	43.4 (37.2, 48.9)
Cervical, vulvar, and vaginal disease[‡†]	7,024	208	8.4	7,022	354	14.4	84.2 (67.8, 92.2)
Mostly HPV Naive	3,032	1	0.1	3,076	67	6.1	98.5 (92.1, 99.9)
Not HPV Naive	3,992	207	15.0	3,946	287	21.2	29.1 (15.2, 41.0)
Low-grade disease[§†]	7,024	128	5.1	7,022	255	10.3	84.0 (67.2, 92.2)
Mostly HPV Naive	3,032	1	0.1	3,076	55	5.0	98.2 (90.1, 99.9)
Not HPV Naive	3,992	127	9.1	3,946	200	14.5	37.6 (21.9, 50.5)
High-grade disease[¶†]	7,024	129	5.2	7,022	155	6.2	80.6 (33.7, 94.3)
Mostly HPV Naive	3,032	0	0.0	3,076	20	1.8	100 (81.5, 100)
Not HPV Naive	3,992	129	9.2	3,946	135	9.7	5.2 (-21.5, 26.1)

[†] The rate is the number of subjects with the end point per 1000 person-years at risk.

[‡] Includes any grade or severity of the indicated disease.

[§] Low-grade disease includes any of CIN 1, condyloma, VIN 1 and VaIN 1.

[¶] High-grade disease includes any of CIN 2/3, AIS, cervical cancer, VIN 2/3, vulvar cancer, VaIN 2/3, and vaginal cancer.

[‖] Vaccine efficacy shown is the sample size-weighted average of the vaccine efficacy in the mostly HPV naive and the not HPV naive subgroups. The mostly-HPV-naive subgroup consists of subjects who at Day 1 were negative for squamous intraepithelial lesions, were seronegative for the 9 vaccine-HPV types, and PCR-negative for the 14 HPV types tested during the study. The non-HPV-naive subgroup consists of those who are not in the mostly-HPV-naive subgroup.

Subjects were counted only once within each applicable row. Some subjects were counted in more than one row.

N = Number of subjects randomized who received at least 1 dose of vaccination and eligible for inclusion in the analysis of efficacy

AIS = Adenocarcinoma in situ; CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; NA = Not available (i.e., not calculable); VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia; SIL = squamous epithelial lesion.

The incidence of high grade cervical, vulvar, and vaginal disease among all participants, irrespective of results on HPV testing, was 14.0 per 1000 person-years in both the 9vHPV group and the qHPV group.

The rates in the subgroup that was not HPV-infected were 2.4 in the 9vHPV group and 4.2 in the qHPV group (efficacy of the 9vHPV vaccine, 42.5%; 95% confidence interval [CI], 7.9 to 65.9).

In that subgroup, the efficacy for disease related to the vaccine HPV types was 100% (95% CI, 70.4 to 100), and the efficacy for disease not related to the vaccine HPV types was 19.7% (95% CI, −34.5 to 52.5).

The modified intention-to-treat analyses of the efficacy of the 9vHPV vaccine against diseases associated with the vaccine HPV types revealed that all cases of high-grade disease detected in the 9vHPV group occurred in participants who were HPV-infected at baseline, which underscores the importance of vaccination before exposure to HPV.

The statistical criterion for non-inferiority with respect to GMT required that the lower bound of the 95% CI for the fold-difference in anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs (9vHPV vaccine vs. qHPV vaccine) be above 0.67, to exclude a decrease of 1.5-fold or more. This criterion was met.

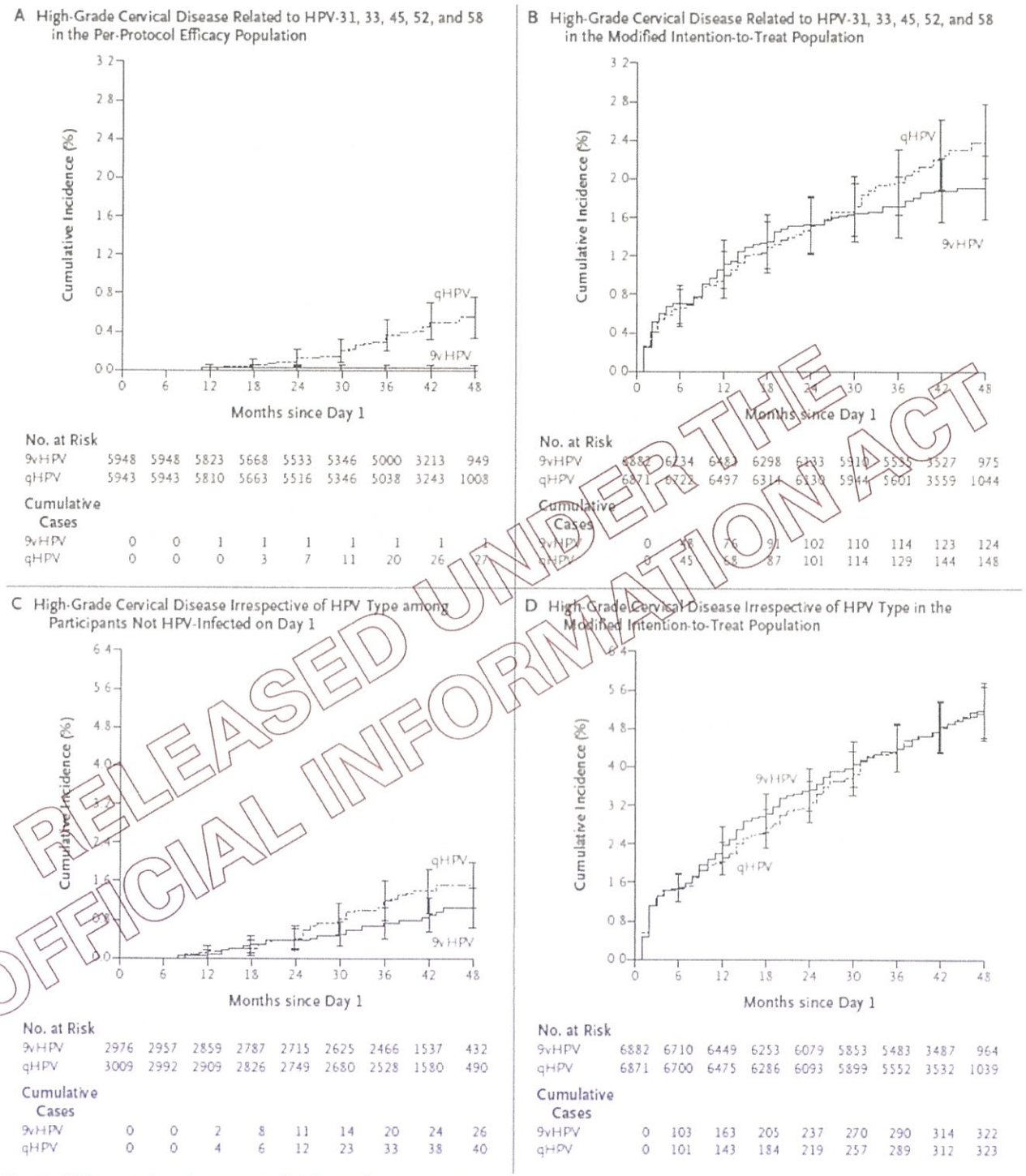


Figure 5 Time to development of high grade cervical disease

A limitation of the current study is the lack of a placebo control group. Given the efficacy of HPV L1 virus-like particle-based vaccination, few disease end points associated with HPV-6, 11, 16, and 18 were expected in either vaccine group, a fact that precluded a direct comparison of the 9vHPV and qHPV vaccines for these vaccine types. With respect to the end points related to HPV-31, 33, 45, 52, and 58, the efficacy of the 9vHPV vaccine was determined on the basis of comparison with the qHPV vaccine group rather than with an unvaccinated population.

Since the qHPV vaccine provides some cross-protection against these HPV types (especially HPV 31), the efficacy of the 9vHPV vaccine may have been underestimated.

Table 14 Geometric mean titres at month 7 in the per-protocol immunogenicity population

Anti-HPV Type	9vHPV Vaccine (N=6792)		qHPV Vaccine (N=6795)		GMT Ratio (95% CI)
	Participants	GMT	Participants	GMT	
	no.	*mMU/ml*	*no.*	*mMU/ml*	
Anti-HPV-6	3993	893.1	3975	875.2	1.02 (0.99 to 1.06)
Anti-HPV-11	3995	666.3	3982	830.0	0.80 (0.77 to 0.83)
Anti-HPV-16	4032	3131.1	4062	3156.6	0.99 (0.96 to 1.03)
Anti-HPV-18	4539	804.6	4541	678.7	1.19 (1.14 to 1.23)
Anti-HPV Response	**9vHPV Vaccine (N=6792)**		**qHPV Vaccine (N=6795)**		**Difference (95% CI)**
	Participants	Seroconversion	Participants	Seroconversion	
	no.	*no. (%)*	*no.*	*no. (%)*	*percentage points*
HPV-6 cLIA ≥30 mMU/ml	3993	3985 (99.8)	3975	3969 (99.8)	0 (-0.3 to 0.2)
HPV-11 cLIA ≥16 mMU/ml	3995	3994 (100)	3982	3980 (99.9)	0 (-0.1 to 0.2)
HPV-16 cLIA ≥20 mMU/ml	4032	4031 (100)	4062	4060 (100)	0 (-0.1 to 0.2)
HPV-18 cLIA ≥24 mMU/ml	4539	4532 (99.8)	4541	4528 (99.7)	0.1 (-0.1 to 0.4)

* The per-protocol immunogenicity population included participants in the per-protocol efficacy population who received three doses of vaccine during prespecified visit intervals and from whom the 7-month serum sample was obtained within a prespecified interval. P<0.001 for all comparisons between the 9vHPV vaccine and the qHPV vaccine. A test of the noninferiority of the 9vHPV vaccine to the qHPV vaccine with respect to GMT required the demonstration that the GMT with the 9vHPV vaccine was lower than the GMT with the qHPV vaccine by no more than a factor of 1.5 or, equivalently, that the lower boundary of the 95% confidence interval of the GMT ratio (9vHPV:qHPV) was greater than 0.67. The GMT, GMT ratio, and P values for the between-group differences in GMT were calculated with the use of analysis-of-variance models. A successful noninferiority test for seroconversion required the demonstration of a statistically significant difference between 9vHPV and qHPV of no more than 5 percentage points or, equivalently, a lower boundary of the 95% confidence interval for the difference in percentages that was greater than −5%. The 95% confidence interval for the difference and the P values for seroconversion were calculated with the use of the Miettinen and Nurminen method. The term cLIA denotes competitive Luminex immunoassay, and mMU milli-Merck units (arbitrary units, defined in the Supplementary Appendix).

The authors concluded that the results of this study showed that the prophylactic administration of 9vHPV vaccine prevented infection and disease associated with the vaccine HPV types. The effect of vaccination on the burden of cancer remains to be determined.

Medsafe comment

Gardasil 9 was as immunogenic as Gardasil for HPV types 6, 11, 16 and 18. It is therefore expected that the long-term efficacy noted above for Gardasil will apply equally to Gardasil 9. Gardasil shows some cross-protection for HPV types in Gardasil 9 in some subjects. Since this was a comparator study the measure of effectiveness of Gardasil 9 was possibly falsely reduced. This is discussed further below.

Measures of efficacy for Gardasil 9 are difficult due to the comparative nature of the clinical trials.[7] The measure of vaccine efficacy on the endpoint irrespective of HPV is ambiguous and difficult to interpret.

Estimating 9vHPV efficacy based on all cases of disease compared to 4vHPV gives an efficacy of 21.4%. Table 15 shows the deconstruction of this estimate. The difference between the deconstruction methods was that patients could be counted more than once in the unconditional method (if they had more than one relevant outcome).

The vaccine efficacy of 92.4% associated with the endpoint in category C1 represents the percent reduction in risk of becoming a case of disease related to HPV types covered by the 9vHPV vaccine in the 9vHPV vaccination group relative to the risk among 4vHPV vaccinated subjects.

The incidence rates of 156.5 and 134.3 per 10,000 person-years for the 9vHPV and 4vHPV vaccine groups, respectively, for the endpoint category C2 represents the incidence of disease related to the

non-vaccine HPV types among subjects who never became a case of disease related to 9vHPV vaccine types. A case count of the C2 endpoint that is higher in the 9vHPV vaccine group compared to 4vHPV vaccine group, which is mostly driven by the trend in the C2.1 category, can be explained both heuristically and rigorously based on the Bayes' rule.

Table 15 Efficacy of 9vHPV compared to 4vHPV against any grade of cervical, vulvar and vaginal disease in the mostly HPV naïve (MHN) analysis population

	9vHPV vaccine (N = 3032)[†]		4vHPV vaccine (N = 3077)[†]		Vaccine efficacy % (95% CI)
Endpoint	Cases	Rate[‡]	Cases	Rate[‡]	
Irrespective of HPV	179	162.0	230	206.0	21.4 (4.6, 35.7)
Deconstruction of the irrespective of HPV endpoint					
Unconditional method					
U1. Related to any 9 vaccine HPV types[§]	6	5.4	80	71.6	92.4 (83.7, 96.8)
U2. Not related to any 9 vaccine HPV types	174	157.3	196	174.6	9.9 (−11.1, 27.0)
U2.1 Related to any of 5 non-vaccine HPV types[¶]	121	-	125	-	-
U2.2 Causal HPV type unknown	64	-	82	-	-
Conditional Method					
C1. Related to any 9 vaccine HPV types[§]	6	5.4	80	71.6	92.4 (83.7, 96.8)
C1.1 Also became a case related to any of 5 non-vaccine HPV types[¶]	1	-	42	-	-
C1.2 Did not become a case related to any of 5 non-vaccine HPV types	5	-	38	-	-
C2. Not related to any 9 vaccine HPV types	173	156.5	150	134.3	16.5 (−46.0, 6.9)
C2.1 Related to any of 5 non-vaccine HPV types[¶]	120	108.6	83	74.3	46.1 (−95.6, −10.9)
C2.2 Causal HPV type unknown	53	48.0	67	60.0	20.1 (−16.3, 45.3)

[†] Number of subject randomized to the indicated vaccination group who received at least 1 injection of vaccine and eligible for inclusion in the MHN analysis population.
[‡] Estimated number of cases per 10,000 person-years.
[§] Count of cases represents subjects who during the study became an endpoint case related to any of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.
[¶] Count of cases represents subjects who during the study became an endpoint case related to any of HPV types 35, 39, 51, 56, and 59. These are the 5 non-vaccine HPV types that were tested during the study, in addition to the testing of the 9 vaccine HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Subjects who never became a case of disease related to 9vHPV vaccine types are the at-risk set for the endpoints in category C2. Let nC2(9v) and nC2(4v) denote the size of this at-risk set in the 9vHPV and 4vHPV vaccine groups, respectively. It is expected that nC2(9v) will be greater than nC2(4v) because there will be more subjects in the 9vHPV vaccine group who never became a case of disease related to 9vHPV vaccine types. Let p(9v) and p(4v) denote the marginal risk (or unconditional probability) of becoming a case of disease not related to any of the 9 vaccine HPV types in the 9vHPV and 4vHPV vaccine groups, respectively. p(9v) and p(4v) are estimated at 0.06 (174/3032 and 196/3077), respectively. Therefore, the expected C2 case counts in the 9vHPV vaccine group denoted by nC2(9v)multiplied by p(9v) are expected to be greater than the corresponding expected case counts in the 4vHPVvaccine group, denoted by nC2(4v) ·p(4v). The higher incidence of the C2 endpoint in the 9vHPV vaccine group compared to 4vHPV vaccine group that results in negative estimates of vaccine efficacy is actually further validation of the efficacy of the 9vHPV vaccine.

Using the Bayes' rule and the case counts provided in Table 15, it can be shown that when the 9vHPV vaccine group is highly efficacious relative to the 4vHPV vaccine group with respect to the C1 endpoints, P(C2.1) in the 9vHPV and 4vHPV vaccine groups are 0.040 and 0.028, respectively; and the expected number of C2.1 events corresponding to these probabilities was 120 and 85 respectively.

By heuristic reasoning and probability calculations, the case counts and incidence rate of endpoints in the C2 category are expected to be higher in the 9vHPV vaccine group compared to the 4vHPV vaccine group when the 9vHPV vaccine is highly efficacious compared to the 4vHPV vaccine with respect to vaccine HPV type-related endpoints (i.e., endpoints in the C1 or U1 category); and when 9vHPV vaccine has no prophylactic cross-protection efficacy relative to the 4vHPV vaccine with respect to non-vaccine HPV type-related endpoints. Thus the negative estimate of vaccine efficacy in the C2 endpoint is a consequence of the high prophylactic efficacy with respect to vaccine HPV type-related endpoints and no cross-protection efficacy with respect to non-vaccine HPV type-related endpoints, of the 9vHPV vaccine relative to the 4vHPV vaccine.

Therefore, the measure of vaccine efficacy in the irrespective of HPV endpoint is being pulled simultaneously in opposite directions by a high positive number and a negative number. As such, the resulting measure of vaccine efficacy in the irrespective of HPV endpoint, when calculated in the

context of data from a clinical trial, is difficult to interpret and its magnitude masks the high efficacy of the innovator vaccine relative to the control vaccine.

3.3.2 Protocol V503-002: Immunological bridging study [8]

In this study findings in young women were bridged to girls and boys aged 9-15 years. Subjects (N = 3066) received a 3-dose regimen of 9vHPV vaccine administered at day 1, month 2, and month 6. Anti-HPV serologic assays were performed at day 1 and month 7.

At 4 weeks after dose 3, 99% of girls, boys, and young women seroconverted for each vaccine HPV type. Increases in geometric mean titres to HPV types 6/11/16/18/ 31/33/45/52/58 were elicited in all vaccine groups. Responses in girls and boys were non-inferior to those of young women. Persistence of anti-HPV responses was demonstrated through 2.5 years after dose 3.

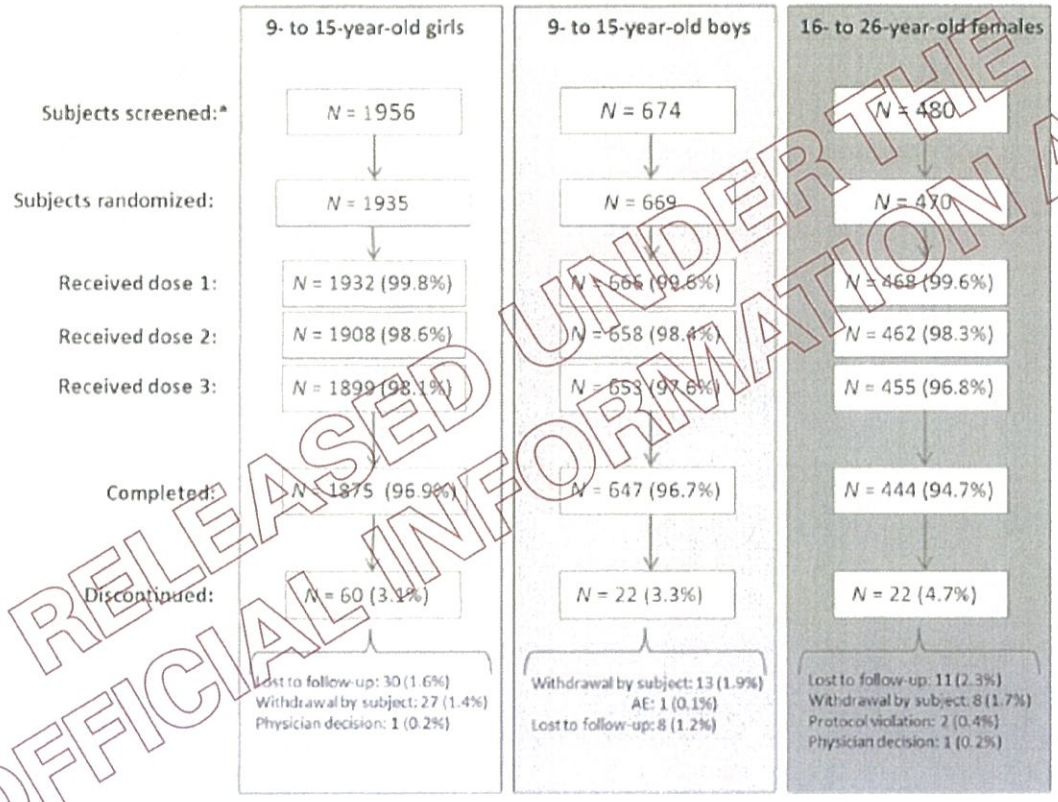


Figure 6 Disposition of subjects.

Table 16 Non-inferiority of GMTs at month 7 in the PPI population

Assay (cLIA)	Girls (9–15 Years Old) (*N* = 646)		Boys (9–15 Years Old) (*N* = 666)		Young Women (16–26 Years Old) (*N* = 468)		GMT Ratio (95% CI)[a]	
	n	GMT, mMU/mL	*n*	GMT, mMU/mL	*n*	GMT, mMU/mL	Girls:Young Women	Boys:Young Women
Anti-HPV 6	517	1715.4	559	2084.7	328	900.8	1.90 (1.70–2.14)	2.31 (2.07–2.59)
Anti-HPV 11	517	1295.1	559	1487.1	332	706.6	1.83 (1.63–2.06)	2.10 (1.88–2.36)
Anti-HPV 16	529	6979.8	569	8628.9	329	3522.6	1.98 (1.77–2.22)	2.45 (2.19–2.74)
Anti-HPV 18	531	2153.7	567	2822.8	345	882.7	2.44 (2.13–2.80)	3.20 (2.80–3.65)
Anti-HPV 31	522	1891.6	564	2221.2	340	753.9	2.51 (2.21–2.85)	2.95 (2.60–3.34)
Anti-HPV 33	534	980.4	567	1198.7	354	466.8	2.10 (1.87–2.36)	2.57 (2.29–2.88)
Anti-HPV 45	534	714.4	570	907.0	368	272.2	2.62 (2.27–3.03)	3.33 (2.89–3.84)
Anti-HPV 52	533	932.9	568	1037.8	337	419.6	2.22 (1.97–2.51)	2.47 (2.19–2.79)
Anti-HPV 58	531	1286.7	566	1567.7	332	590.5	2.18 (1.93–2.45)	2.66 (2.37–2.98)

Analyses in a subset of all study sites may be conducted for regulatory purposes. mMU, milli Merck units. *N*, number of subjects assigned to the respective vaccination group who received at least 1 injection; *n*, number of subjects contributing to the analysis. The per-protocol immunogenicity (PPI) population included subjects who were seronegative at day 1 (and for young women PCR-negative from day 1 through month 7) to the HPV type being analyzed, who received 3 doses of vaccine during prespecified visit intervals, and from whom the month 7 sample was obtained within a prespecified interval.

[a] The *P* value for noninferiority was < .001 for all comparisons.

Table 17 Summary of anti HPV cLIA GMTs over time

Assay (cLIA) and Time Point	9vHPV Vaccine			
	Girls (9–15 Years Old)		Boys (9–15 Years Old)	
	n	GMT (95% CI), mMU/mL	*n*	GMT (95% CI), mMU/mL
Anti HPV 6				
Day 1	1597	<16 (<16, <16)	559	<16 (<16, <16)
Month 07	1597	17120 (16389–17884)	559	20847 (19409–22392)
Month 12	437	616.1 (571.3–664.5)	491	692.4 (639.9–749.3)
Month 24	416	312.9 (288.7–339.2)	470	336.6 (310.8–364.6)
Month 36	407	252.8 (232.1–275.3)	457	262.7 (241.4–285.8)
Anti HPV 11				
Day 1	1597	<6 (<6, <6)	559	<6 (<6, <6)
Month 07	1597	1278.7 (1223.1–1336.8)	559	1487.1 (1385.0–1596.7)
Month 12	439	393.3 (360.4–429.1)	495	456.6 (419.2–497.4)
Month 24	418	179.7 (163.6–197.5)	471	201.1 (183.7–220.2)
Month 36	411	145.8 (132.6–160.2)	463	156.6 (142.4–172.1)
Anti HPV 16				
Day 1	1627	<12 (<12, <12)	569	<12 (<12, <12)
Month 07	1627	7071.6 (6776.1–7380.1)	569	8628.9 (8077.5–9218.0)
Month 12	444	2428.5 (2256.0–2614.2)	505	2847.1 (2639.5–3071.0)
Month 24	423	1078.7 (985.8–1180.3)	481	1230.8 (1126.3–1345.1)
Month 36	416	857.4 (779.8–942.8)	472	944.1 (856.4–1040.8)
Anti HPV 18				
Day 1	1641	<8 (<8, <8)	567	<8 (<8, <8)
Month 07	1641	2081.2 (1978.8–2188.8)	567	2822.8 (2608.0–3054.2)
Month 12	446	494.1 (445.3–548.2)	503	769.2 (699.1–846.3)
Month 24	425	210.3 (188.1–234.8)	479	317.3 (286.7–351.1)
Month 36	418	167.8 (149.5–188.3)	470	244.2 (219.1–272.2)
Anti HPV 31				
Day 1	1617	<4 (<4, <4)	564	<4 (<4, <4)
Month 07	1617	1879.3 (1781.3–1971.6)	564	2221.2 (2056.4–2399.1)
Month 12	443	574.1 (521.5–632.2)	500	689.4 (628.1–756.7)
Month 24	421	252.2 (226.2–281.2)	476	300.2 (270.3–333.3)
Month 36	414	216.6 (194.0–241.8)	467	246.3 (221.4–274.1)
Anti HPV 33				
Day 1	1637	<4 (<4, <4)	567	<4 (<4, <4)
Month 07	1637	944.1 (904.3–985.7)	567	1198.7 (1117.3–1285.9)
Month 12	441	278.2 (255.5–302.9)	503	368.8 (338.6–401.6)
Month 24	419	115.6 (104.5–127.8)	479	151.5 (137.6–166.8)
Month 36	412	94.1 (84.9–104.2)	471	120.8 (109.3–133.6)
Anti HPV 45				
Day 1	1647	<3 (<3, <3)	570	<3 (<3, <3)
Month 07	1647	737.1 (698.4–777.8)	570	907.0 (830.0–991.2)
Month 12	448	195.2 (174.3–218.5)	506	254.1 (227.6–283.7)
Month 24	426	77.3 (68.2–87.5)	482	99.5 (88.1–112.5)
Month 36	419	64.7 (57.1–73.4)	473	76.7 (67.4–87.1)
Anti HPV 52				
Day 1	1642	<3 (<3, <3)	568	<3 (<3, <3)
Month 07	1642	970.5 (927.1–1016.0)	568	1037.8 (962.9–1118.6)
Month 12	448	295.3 (270.3–322.7)	505	313.3 (285.6–343.6)
Month 24	426	134.7 (122.7–148.0)	481	136.3 (124.1–149.7)
Month 36	419	109.6 (99.7–120.4)	472	104.9 (94.9–115.8)
Anti HPV 58				
Day 1	1630	<4 (<4, <4)	566	<4 (<4, <4)
Month 07	1630	1277.7 (1222.0–1336.0)	566	1567.7 (1461.2–1682.0)
Month 12	446	424.0 (390.1–460.9)	502	526.9 (483.7–574.0)
Month 24	424	178.0 (161.5–196.3)	478	220.7 (201.0–242.3)
Month 36	417	147.4 (133.0–163.2)	470	170.9 (154.5–189.0)

mMU, milli Merck units; *n*, number of subjects contributing to the analysis

Medsafe comment
The same bridging strategy used for Gardasil was used here. Immunogenicity is greater in those under 15 years of age. The response was comparable between girls and boys.

3.3.3 Protocol V503-003 Phase III study to evaluate the immunogenicity and tolerability of 9vHPV in men 16 to 26 years compared to women 16 to 26 years. [9]

This study was designed to evaluate the immunogenicity and tolerability of a prophylactic 9-valent HPV (types 6/11/16/18/31/33/45/52/58) VLP (9vHPV) vaccine in young men 16–26 years of age in comparison to young women 16–26 years of age (the population that was used to establish 9vHPV vaccine efficacy). Safety and immunogenicity data from this study were used to bridge 9vHPV vaccine efficacy findings in 16–26 year old women to 16–26 year old men.

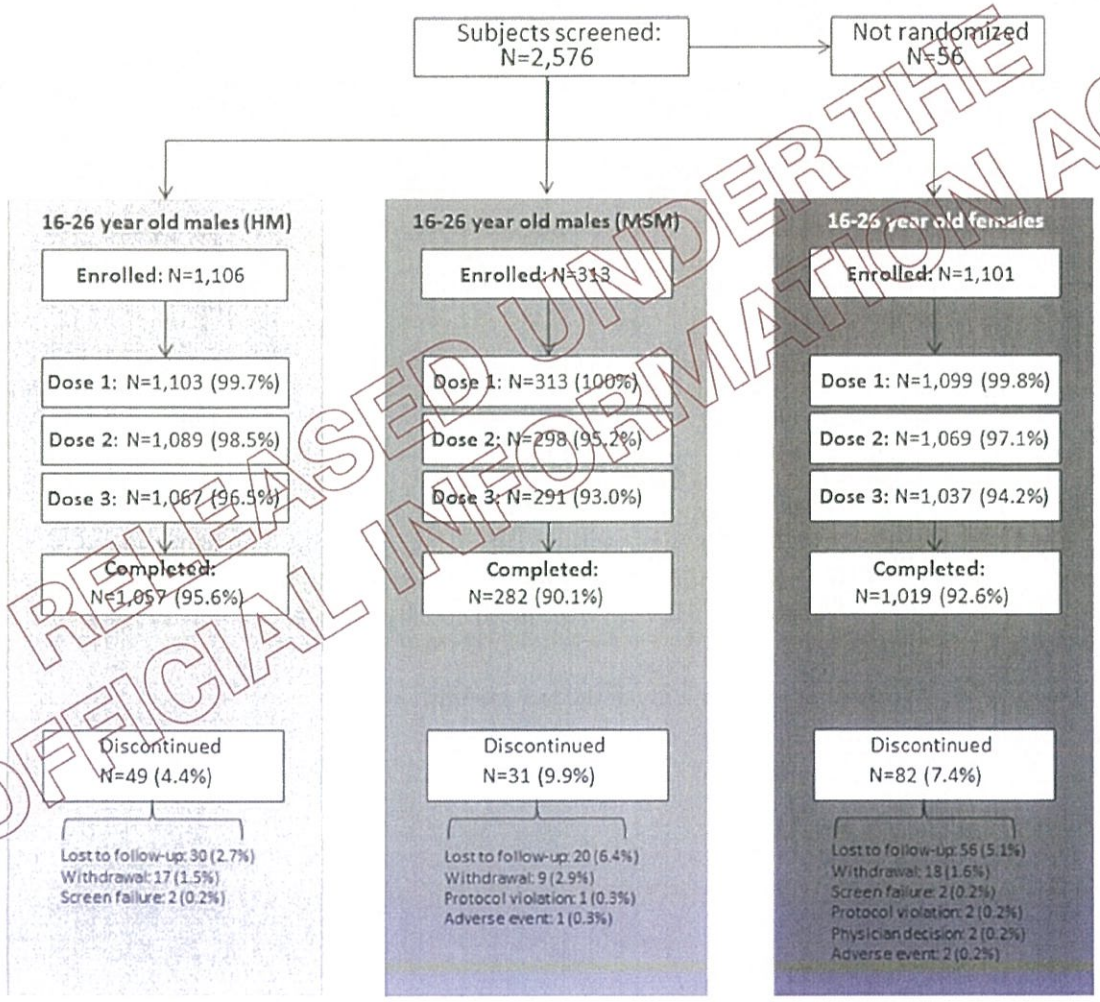


Figure 7 Disposition of subjects

Immunogenicity was evaluated in a per-protocol population of subjects. Each vaccine component was analysed separately. To be included in the primary immunogenicity analysis for the HPV 6 and HPV 11 components, subjects had to be seronegative to both HPV6 and 11 at day 1 (because of extensive cross-reactivity due to the high amino acid sequence identity [92%] between HPV 6 and HPV11 L1 proteins).

The primary immunogenicity objective of the study was to demonstrate that administration of the 9vHPV vaccine induces non-inferior month 7 GMTs for serum anti-HPV 6, anti-HPV 11, anti-HPV 16,

anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 in heterosexual men (HM) 16–26 years of age compared with young women 16–26 years of age.

Separately for each anti-HPV type, the 95% CI of GMT ratio was derived from an ANOVA model with the log of antibody titres as the response and vaccination group as the fixed effect.

With the planned sample size, this study had over 90% power for the primary immunogenicity hypothesis on all nine HPV types for a true GMT ratio of at least 0.875 and a standard deviation of 1.2 on the log scale for all nine types, assuming an exclusion rate from the per-protocol analyses of 30% for women and 40% for HM.

This study enrolled 1106 heterosexual men (HM) and 1101 women who had not yet received HPV vaccination. In addition, 313 men having sex with men (MSM) were enrolled and were evaluated separately for immunogenicity because previous results showed that antibody responses to qHPV vaccine were lower in MSM than in HM.

All subjects were administered a 3-dose regimen (Day 1, Month 2, Month 6) of 9vHPV vaccine. Serum samples were collected for anti-HPV assays. Safety information was collected for ~12 months.

Table 18 Per-protocol summary of month 7 anti-HPV GMTs

Assay	HM (*N* = 1103)			MSM (*N* = 313)			Women (*N* = 1099)		
	n	GMT (mMU/mL)	95% CI	*n*	GMT (mMU/mL)	95% CI	*n*	GMT (mMU/mL)	95% CI
Anti-HPV 6	847	782.0	(738.0, 828.7)	164	568.9	(498.7, 649.0)	708	703.9	(660.6, 749.9)
Anti-HPV 11	851	616.7	(582.4, 653.0)	165	435.7	(384.4, 498.5)	712	564.9	(530.6, 601.3)
Anti-HPV 16	899	3346.0	(3158.9, 3544.1)	212	2294.0	(2087.8, 2582.5)	781	2788.3	(2621.4, 2965.8)
Anti-HPV 18	906	808.2	(754.9, 865.4)	220	608.1	(529.4, 698.5)	831	679.8	(633.1, 730.1)
Anti-HPV 31	908	708.5	(662.7, 757.6)	227	420.7	(368.0, 480.9)	826	570.1	(531.5, 611.5)
Anti-HPV 33	901	384.8	(362.5, 408.4)	230	252.3	(224.2, 283.8)	853	322.0	(302.9, 342.3)
Anti-HPV 45	909	235.6	(219.0, 253.5)	232	157.5	(136.2, 182.2)	871	185.7	(172.3, 200.2)
Anti-HPV 52	907	386.8	(363.4, 411.6)	232	233.1	(206.0, 263.7)	849	335.2	(314.3, 357.6)
Anti-HPV 58	897	509.8	(479.0, 544.6)	223	319.8	(283.2, 361.0)	839	409.3	(384.5, 435.7)

N = Number of individuals randomized to the respective vaccination group who received at least one vaccination.
n = Number of individuals contributing to the analysis.
GMT = Geometric mean titer; mMU = milli-Merck units; CI = Confidence interval; HPV = Human papillomavirus; HM = heterosexual men; MSM = men having sex with men.

The geometric mean titres (GMTs) for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 for HM were non-inferior to those of women at Month 7 Over 99.5% of subjects were seropositive at Month 7 for each vaccine HPV type. Administration of 9vHPV vaccine to both 16–26 year old men and women was generally well tolerated.

Table 19 Per-protocol analyses of non-inferiority of GMTs at month 7

Assay	HM (*N* = 1103)		Women (*N* = 1099)		HM/women	
	n	GMT (mMU/mL)	*n*	GMT (mMU/mL)	GMT ratio	95% CI
Anti-HPV 6	847	782.0	708	703.9	1.11	(1.02, 1.21)
Anti-HPV 11	851	616.7	712	564.9	1.09	(1.00, 1.19)
Anti-HPV 16	899	3346.0	781	2788.3	1.20	(1.10, 1.30)
Anti-HPV 18	906	808.2	831	679.8	1.19	(1.08, 1.31)
Anti-HPV 31	908	708.5	826	570.1	1.24	(1.13, 1.37)
Anti-HPV 33	901	384.8	853	322.0	1.19	(1.10, 1.30)
Anti-HPV 45	909	235.6	871	185.7	1.27	(1.14, 1.41)
Anti-HPV 52	907	386.8	849	335.2	1.15	(1.05, 1.26)
Anti-HPV 58	897	509.8	839	409.3	1.25	(1.14, 1.36)

* The *p*-value for non-inferiority was <0.001 for all comparisons.
N = Number of individuals randomized to the respective vaccination group who received at least one vaccination.
n = Number of individuals contributing to the analysis.
GMT = Geometric mean titer; mMU = milli-Merck units; CI = Confidence interval; HPV = Human papillomavirus; HM = heterosexual men; MSM = men having sex with men.

The authors consider these results support bridging the efficacy findings with 9vHPV vaccine in young women16–26 years of age to men 16–26 years of age. Seroconversion for each of the nine vaccine HPV types was achieved in>99% of participants in the study.

Antibody response was evaluated separately in HM and MSM. The antibody response to 9vHPV vaccine in HM 16–26 years of age was shown to be non-inferior to those observed in young women 16–26 years of age (the population used to establish 9vHPV vaccine efficacy. Marked antibody responses were observed in MSM as well, however, type-specific antibody responses for all vaccine

HPV types were numerically lower in MSM than in HM and women. Analyses excluded a 2-fold decrease in GMTs between MSM and young women, as well as between MSM and HM.

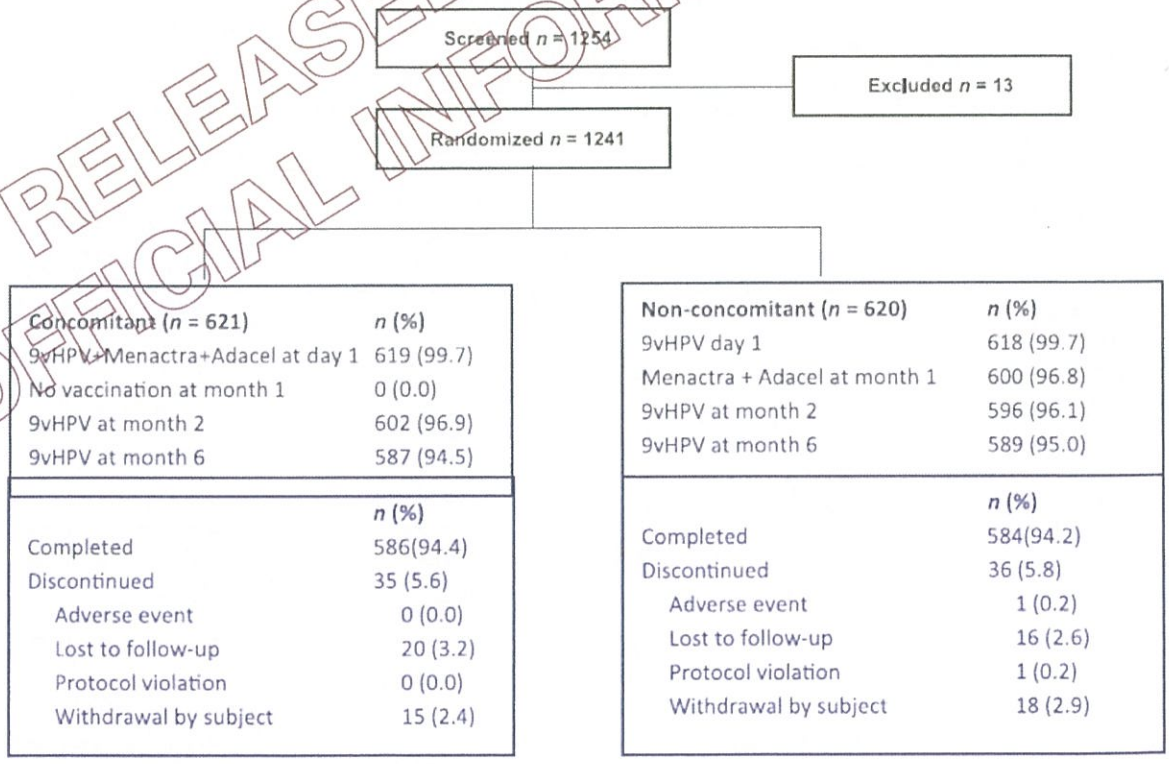
The authors stated that this result is notable given that the study was not powered to conduct a statistical comparison between MSM and the two other groups and the number of MSM in this study was substantially lower than the numbers of HM and women (the two groups for which a non-inferiority comparison was planned). A similar result was previously obtained in the clinical study of qHPV vaccine in men 16–26 years of age. The reason why HPV vaccination induces lower anti-HPV anti-body response in MSM than in HM is not understood. MSM included in immunogenicity analyses were HIV negative. MSM appeared to have substantially more prior exposure to HPV than HM (as judged by the HPV seropositivity rates at day 1) which might influence their immune response to subsequent HPV vaccination.

Medsafe comment

This study bridged the efficacy in women to men via immunological analyses as performed for younger age groups. Since the effective antibody level is unknown, but possibly below the detection level of the assay it is assumed that the lower antibody levels achieved in MSM are still protective.

3.3.4 Protocol V503-005 Phase III randomised multicentre comparative study of 9vHPV vaccine in children 11 to 15 years receiving concomitant Menactra and Adacel. [10]

This study in 11- to 15-year-old boys and girls compared the immunogenicity and safety of GARDASIL 9 administered either concomitantly or non-concomitantly with 2 vaccines routinely administered in this age group (Menactra [MCV4; Neisseria meningitidis serotypes A/C/Y/W-135] or Adacel [Tdap; diphtheria/tetanus/acellular pertussis]).



Concomitant (*n* = 621)	*n* (%)
9vHPV+Menactra+Adacel at day 1	619 (99.7)
No vaccination at month 1	0 (0.0)
9vHPV at month 2	602 (96.9)
9vHPV at month 6	587 (94.5)

	n (%)
Completed	586(94.4)
Discontinued	35 (5.6)
Adverse event	0 (0.0)
Lost to follow-up	20 (3.2)
Protocol violation	0 (0.0)
Withdrawal by subject	15 (2.4)

Non-concomitant (*n* = 620)	*n* (%)
9vHPV day 1	618 (99.7)
Menactra + Adacel at month 1	600 (96.8)
9vHPV at month 2	596 (96.1)
9vHPV at month 6	589 (95.0)

	n (%)
Completed	584(94.2)
Discontinued	36 (5.8)
Adverse event	1 (0.2)
Lost to follow-up	16 (2.6)
Protocol violation	1 (0.2)
Withdrawal by subject	18 (2.9)

Figure 8 Disposition of subjects

Participants received 9vHPV vaccine at day 1 and months 2 and 6; the concomitant group (n = 621) received MCV4/Tdap concomitantly with 9vHPV vaccine at day 1; the non-concomitant group (n = 620) received MCV4/Tdap at month 1. Antibodies to HPV-, MCV4-, and Tdap-relevant antigens were

determined. Injection-site and systemic adverse events (AEs) were monitored for 15 days after any vaccination; serious AEs were monitored throughout the study.

Table 20 Non-inferiority criteria corresponding to the primary hypothesis related to immunogenicity

Antigen	Parameter[a]	Expected Rates/SDs	Noninferiority Margin	Power
HPV type 6, 11, 16, 18, 31, 33, 45, 52, 58[b]	GMT	σ = 1.2	Twofold decrease	>99.9%
N meningitidis Serogroup A	% with fourfold or greater rise in titer	90%	10 percentage points	99.8%
N meningitidis Serogroup C	% with fourfold or greater rise in titer	90%	10 percentage points	99.8%
N meningitidis Serogroup Y	% with fourfold or greater rise in titer	80%	10 percentage points	95.1%
N meningitidis Serogroup W-135	% with fourfold or greater rise in titer	95%	10 percentage points	>99.9%
Diphtheria	% with titer >0.1 IU/mL	95%	10 percentage points	>99.9%
Tetanus	% with titer >0.1 IU/mL	92%	10 percentage points	99.8%
Pertussis PT	GMT	σ = 1.0	1.5-fold decrease	>99.9%
Pertussis FHA	GMT	σ = 0.8	1.5-fold decrease	>99.9%
Pertussis PRN	GMT	σ = 1.3	1.5-fold decrease	>99.9%
Pertussis FIM	GMT	σ = 1.5	1.5-fold decrease	97.0%

[a] Noninferiority of anti-HPV GMTs was measured at 4 weeks after dose 3 of 9vHPV vaccine. Noninferiority of *N. meningitidis* serogroups A/C/Y-W-135, diphtheria, tetanus, and pertussis was measured 4 weeks postvaccination with MCV4 and Tdap.

[b] Each HPV type is tested separately.

The

- geometric mean titres for all HPV types in 9vHPV vaccine 4 weeks after dose 3,
- proportion of subjects with a fourfold rise or greater in titres for 4 N meningitidis serotypes 4 weeks after injection with MCV4,
- proportion of subjects with antibody titres to diphtheria and tetanus >0.1 IU/mL,
- and geometric mean titres for pertussis antigens 4 weeks after injection with Tdap

were all non-inferior in the concomitant group compared with the non-concomitant group.

Injection-site swelling occurred more frequently in the concomitant group. There were no vaccine-related serious AEs.

Table 21 Anti-HPV GMTs and estimated fold difference at 4 weeks after dose 3 in the HPV per-protocol populations

Antigen	Concomitant (Group A),[a] N = 619		Nonconcomitant (Group B),[a] N = 618		Estimated Fold Difference Group A/Group B[b] (95% Confidence Interval)
	n	Estimated GMT (mMU/mL)	*n*	Estimated GMT (mMU/mL)	
HPV6	501	2198.7	514	2260.7	0.97 (0.88 to 1.08)
HPV11	502	1495.0	514	1547.2	0.97 (0.87 to 1.07)
HPV16	513	8882.6	530	9027.6	0.98 (0.89 to 1.09)
HPV18	516	2610.4	535	2633.9	0.99 (0.88 to 1.12)
HPV31	514	2439.4	536	2334.3	1.04 (0.93 to 1.17)
HPV33	520	1268.5	537	1276.3	0.99 (0.89 to 1.11)
HPV45	523	947.8	539	863.8	1.10 (0.97 to 1.25)
HPV52	521	1082.7	538	1103.7	0.98 (0.88 to 1.10)
HPV58	519	1532.8	537	1555.1	0.99 (0.88 to 1.10)

mMU, milliMerck units. *N*, number of subjects randomized to the respective vaccination group who received ≥1 injection. *n* = number of subjects contributing to the analysis.

[a] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6 and MCV4 and Tdap on day 1; Group B (nonconcomitant administration) received 9vHPV vaccine as Group A and MCV4 and Tdap at month 1.

[b] *P* value for noninferiority <.001 for all 9 antigens. The noninferiority criterion for GMT end points reported in this table was defined as statistically less than a twofold decrease in Group A compared with Group B. Noninferiority of GMT in Group A relative to Group B was demonstrated if the lower limit of the 95% confidence interval for the fold difference was >0.5.

Table 22 Estimated percentage point difference in the per-protocol population for MCV4 for percent of subjects with fourfold or greater rise in titres for *N meningitidius* serogroups at 4 weeks post vaccination

	Concomitant (Group A),[a] *N* = 619			Nonconcomitant (Group B),[a] *N* = 618			Estimated Percentage Point Difference Group A – Group B (97.5% CI)
	m/n	%	97.5% CI	*m/n*	%	97.5% CI	
Serogroup A	466/590	79.0	(75.0 to 82.6)	425/564	75.4	(71.0 to 79.3)	3.8 (−1.7 to 9.3)[b]
Serogroup C	548/590	92.9	(90.1 to 95.1)	538/566	95.1	(92.6 to 96.9)	−2.1 (−5.4 to 1.1)[b]
Serogroup W-135	563/589	95.6	(93.3 to 97.3)	553/566	97.7	(95.9 to 98.9)	−2.1 (−4.7 to 0.3)[b]
Serogroup Y	540/590	91.5	(88.6 to 93.9)	506/566	89.4	(86.1 to 92.1)	2.1 (−1.8 to 6.1)[b]

m = number of subjects with the indicated response; N, number of subjects randomized to the respective vaccination group who received at least 1 injection; n, number of subjects contributing to the analysis. CI, confidence interval.

[a] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6 and MCV4 and Tdap on day 1. Group B (nonconcomitant administration) received 9vHPV vaccine as above and Tdap-IPV vaccine at month 1.

[b] *P* value for noninferiority < .001 for all antigens. The noninferiority criterion for end points reported in this table was defined as statistically <10 percentage points decrease in Group A compared with Group B. Noninferiority of percent of subjects with fourfold or greater rise in titers for *N. meningitidis* serogroups in Group A relative to Group B was demonstrated if the lower limit of the 97.5% CI for the percentage point difference was greater than −10.

Table 23 Estimated percentage point difference in the per-protocol population of subjects with diphtheria and tetanus titres ≥ 0.1IU/ml at 4 weeks post vaccination

	Concomitant (Group A),[a] *N* = 619			Nonconcomitant (Group B),[a] *N* = 618			Estimated Percentage Point Difference Group A – Group B (97.5% CI)
	m/n	%	97.5% CI	*m/n*	%	97.5% CI	
Diphtheria titer ≥0.1 IU/mL							
Day 1	403/593	68.0	(63.5 to 72.2)	391/564	69.3	(64.8 to 73.6)	
4 wk postvaccination	595/595	100	(99.3 to 100)	566/566	100	(99.2 to 100)	0.0 (−0.8 to 0.9)[b]
Tetanus titer ≥0.1 IU/mL							
Day 1	460/573	80.3	(76.3 to 83.9)	450/548	82.1	(78.1 to 85.6)	
4 wk postvaccination	593/594	99.8	(98.9 to 100)	562/562	100	(99.2 to 100)	−0.2 (−1.2 to 0.7)[b]

m = number of subjects with the indicated response; N, number of subjects randomized to the respective vaccination group who received at least 1 injection; n, number of subjects contributing to the analysis. CI, confidence interval.

[a] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6 and MCV4 and Tdap on day 1. Group B (nonconcomitant administration) received 9vHPV vaccine as Group A and Tdap-IPV vaccine at month 1.

[b] *P* value for non-inferiority <0.001 for all antigens. The noninferiority criterion for endpoints reported in this table was defined as statistically less than 10 percentage points decrease in Group A compared with Group B. Non-inferiority of percent with titer ≥ 0.1 IU/mL in Group A relative to Group B was demonstrated if the lower limit of the 97.5% CI for the percentage point difference was greater than −10.

Table 24 Antipertussis GMTs and estimated fold difference at 4 weeks post vaccination in the per-protocol population for dTap

	Concomitant (Group A),[a] *N* = 619			Nonconcomitant (Group B),[a] *N* = 618			Estimated Fold Difference Group A/Group B (97.5% CI)
	n	Estimated GMT (ELU/ml)	97.5% CI	*n*	Estimated GMT (ELU/ml)	97.5% CI	
Anti-PT							
Day 1	594	7.5	(6.8 to 8.2)	564	7.1	(6.5 to 7.8)	
4 wk postvaccination	595	28.5	(25.8 to 31.5)	566	35.7	(32.3 to 39.6)	0.80 (0.69 to 0.92)[b]
Anti-FHA							
Day 1	594	33.0	(30.4 to 35.8)	564	32.8	(30.1 to 35.7)	
4 wk postvaccination	595	184.1	(171.8 to 197.4)	566	201.4	(187.6 to 216.3)	0.91 (0.83 to 1.01)[b]
Anti-PRN							
Day 1	594	20.9	(19.2 to 22.8)	564	20.4	(18.6 to 22.4)	
4 wk postvaccination	595	328.4	(300.6 to 358.8)	566	344.0	(314.2 to 376.7)	0.95 (0.84 to 1.08)[b]
Anti-FIM							
Day 1	594	16.1	(14.3 to 18.2)	564	15.8	(13.9 to 18.1)	
4 wk postvaccination	595	653.0	(556.0 to 767.1)	566	681.4	(577.8 to 803.7)	0.96 (0.76 to 1.21)[b]

N, number of subjects randomized to the respective vaccination group who received at least 1 injection; n, number of subjects contributing to the analysis. CI, confidence interval.

[a] Group A (concomitant administration) received a 0.5-mL dose of 9vHPV vaccine at day 1, month 2, and month 6 and MCV4 and Tdap on day 1. Group B (nonconcomitant administration) received 9vHPV vaccine as Group A and Tdap-IPV vaccine at month 1.

[b] *P* value for noninferiority <.001 for all antigens with the exception of anti-pertussis toxin, where *P* for noninferiority was .003. The noninferiority criterion for end points reported in this table was defined as statistically <1.5-fold decrease in Group A compared with Group B. Noninferiority of GMT in Group A relative to Group B was demonstrated if the lower limit of the 97.5% CI for the fold difference was >0.67.

The authors concluded that concomitant administration of 9vHPV vaccine with MCV4/Tdap was generally well tolerated and did not interfere with the antibody response to any of these vaccines. This strategy would minimize the number of visits required to deliver each vaccine individually. The authors considered that even though only one dTap vaccine was used, it is reasonable to assume that the results may be generalisable to other dTap vaccines.

Medsafe comments

This study did not highlight any problems for co-administration of Gardasil 9 with Menactra or Adacel vaccines. Boostrix is the equivalent to Adacel in the New Zealand immunisation schedule.

3.3.5 Protocol V503-006 Phase III randomised double-blind placebo controlled immunogenicity study of 9vHPV vaccine in prior qHPV vaccine recipients. [11]

V503-006 was a randomized, double-blinded, safety/tolerability and immunogenicity study of the 9vHPV vaccine in females 12–26 years of age who were previously vaccinated with qHPV vaccine. Subjects were randomized in a 2:1 ratio to receive 3 doses of 9vHPV vaccine (n = 618) or saline placebo (n = 306) at day 1, month 2, and month 6. Systemic, injection-site and serious adverse experiences (AEs) were monitored. Serum samples were collected at day 1, month 2, and month 7.

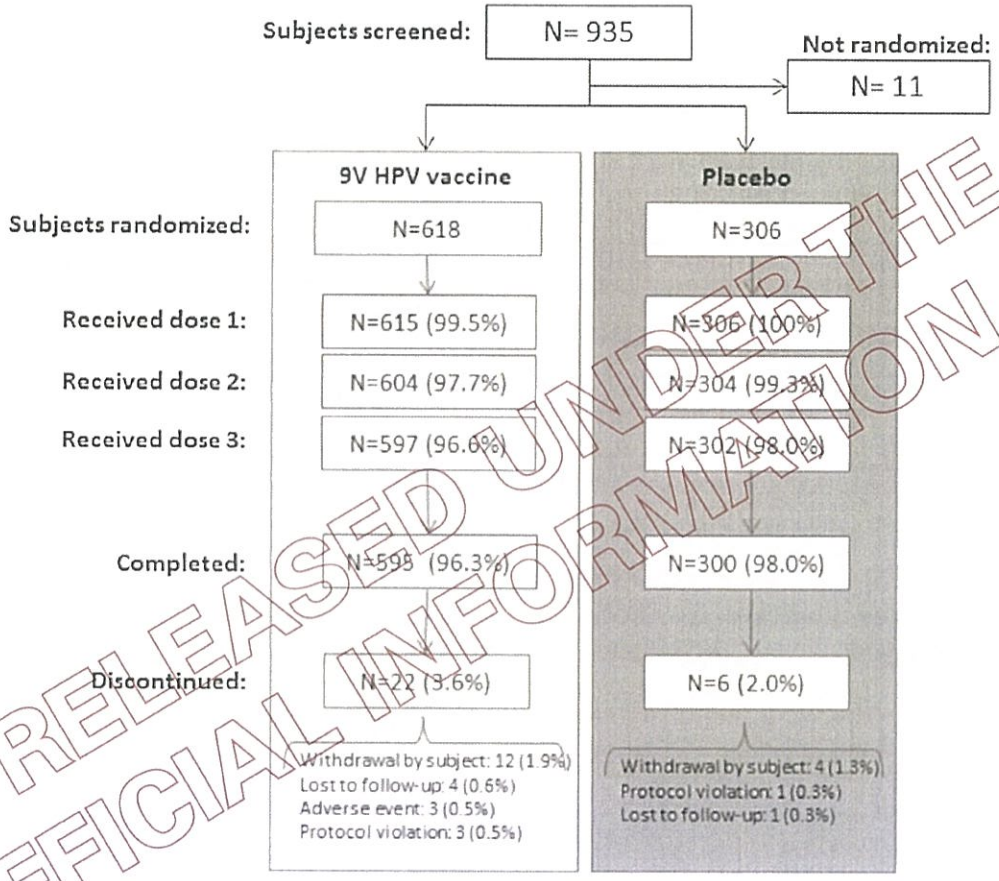


Figure 9 Subject disposition

The frequency of injection-site AEs (days 1–5 following any vaccination) was higher in the 9vHPV vaccine group than in the placebo group (91.1% and 43.9%, respectively). The frequencies of vaccine-related systemic AEs (days 1–15 following any vaccination) were generally comparable between the 2 groups (30.6% in the 9vHPV vaccine group, and 25.9% in the placebo group).

One vaccine-related serious AE was reported in each of the 9vHPV vaccine and placebo groups. Few subjects (9vHPV = 0.5%; placebo = 0%) discontinued due to an AE.

At 4 weeks post-dose 3, over 98% of subjects in the 9vHPV vaccine group were seropositive for HPV types 31/33/45/52/58, with marked elevations in cLIA geometric mean titres (GMTs) to these HPV types.

Injection-site AEs occurred more frequently in the 9vHPV vaccine group than in the placebo group; given that a saline placebo was used, this difference represents the local reactions due to the antigen and adjuvant in the 9vHPV vaccine.

Table 25 Summary of anti-HPA cLIA GMT by vaccination group

Assay (cLIA)	Time point	9vHPV vaccine (N = 615)			Placebo (N = 306)		
		n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6	Day 1	499	348.2	(320.2, 378.8)	248	372.4	(330.6, 419.6)
	Month 02	505	2426.7	(2254.2, 2612.3)	245	363.4	(326.9, 404.0)
	Month 07	511	2207.4	(2052.7, 2373.9)	251	323.8	(291.9, 359.2)
Anti-HPV 11	Day 1	513	253.0	(232.3, 275.6)	261	263.6	(233.8, 297.1)
	Month 02	511	2077.8	(1925.9, 2241.6)	256	253.3	(227.6, 282.0)
	Month 07	515	1824.0	(1695.5, 1962.2)	261	225.4	(203.4, 249.7)
Anti-HPV 16	Day 1	513	1066.1	(973.8, 1167.1)	261	1103.7	(972.2, 1253.1)
	Month 02	511	13,877.6	(12,846.3, 14,991.7)	256	1076.1	(964.9, 1200.1)
	Month 07	515	11,192.8	(10,393.6, 12,053.6)	261	966.9	(871.3, 1072.9)
Anti-HPV 18	Day 1	513	154.2	(135.4, 175.5)	261	136.1	(113.4, 163.2)
	Month 02	511	2187.9	(1975.2, 2423.5)	256	130.1	(112.6, 150.3)
	Month 07	515	2285.8	(2067.4, 2527.3)	261	112.8	(98.0, 129.9)
Anti-HPV 31	Day 1	513	4.1	(<4, 4.5)	261	4.3	(<4, 5.0)
	Month 02	511	201.1	(180.5, 224.0)	256	4.3	(<4, 5.0)
	Month 07	515	260.0	(237.6, 284.5)	261	4.7	(4.1, 5.3)
Anti-HPV 33	Day 1	513	<4	(<4, <4)	261	<4	(<4, <4)
	Month 02	511	70.0	(63.2, 77.4)	256	<4	(<4, <4)
	Month 07	515	175.2	(162.5, 188.9)	261	<4	(<4, <4)
Anti-HPV 45	Day 1	513	<3	(<3, <3)	261	<3	(<3, <3)
	Month 02	511	15.1	(13.5, 16.8)	256	<3	(<3, <3)
	Month 07	515	97.4	(89.8, 105.7)	261	<3	(<3, <3)
Anti-HPV 52	Day 1	513	<3	(<3, <3)	261	<3	(<3, <3)
	Month 02	511	56.0	(51.2, 61.2)	256	<3	(<3, <3)
	Month 07	515	264.1	(244.6, 285.1)	261	<3	(<3, <3)
Anti-HPV 58	Day 1	513	<4	(<4, <4)	261	<4	(<4, <4)
	Month 02	511	83.2	(76.4, 90.5)	256	<4	(<4, <4)
	Month 07	515	269.7	(250.9, 290.0)	261	<4	(<4, <4)

[a] The modified per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, and had a Month 7 serum sample collected within an acceptable day range.
N: number of subjects randomized to the respective vaccination group who received at least 1 injection; *n*: number of subjects contributing to the analysis; CI: confidence interval; cLIA: competitive Luminex Immunoassay; GMT: geometric mean titer; mMU: milliMerck units.

A cross-study comparison of 9vHPV vaccine immunogenicity in prior qHPV vaccine recipients in this study versus subjects with no prior HPV vaccination in the pivotal efficacy study of 9vHPVvaccine (protocol V503-001) revealed that:

(1) Anti-HPV 6/11/16/18 GMTs at month 7 were higher in prior qHPV vaccine recipients; and

(2) anti-HPV 31/33/45/52/58 GMTs at month 7 were lower in prior qHPV vaccine recipients.

These findings indicate that the immunogenicity profile of the 9vHPV vaccine may be different in prior qHPV vaccine recipients compared with subjects without prior HPV vaccination. However, these results should be interpreted with caution, since they are based on non-randomized, cross-study analyses.

Stronger responses to HPV 6/11/16/18 in prior qHPV vaccine recipients are consistent with a memory response which is not surprising since all study participants previously received qHPV vaccine.

Lower responses to HPV 31/33/45/52/58 were interpreted as follows. HPV 31/33/52/58 and HPV 45 L1 proteins share approximately 80% amino acid identity with HPV 16 and HPV 18 L1 proteins, respectively. Thus, lower responses to HPV 31/33/45/52/58 in prior qHPV vaccine recipients are reminiscent of previous observations that a prior antigenic encounter can alter a subsequent response to a related antigen. Such findings were previously reported with various antigens in both human subjects and animal models. Given that memory responses are more vigorous than primary responses, it is likely that memory response to HPV 16/18 L1 proteins would be preferentially activated, resulting in a blunting of primary response to antigenically related HPV 31/33/45/52/58 L1 proteins.

Prior qHPV vaccine recipients who were seropositive at baseline to one of the vaccine HPV types 31/33/45/52/58 (i.e., subjects who were primed and thus able to develop a memory response to this HPV type) had a more robust anti-HPV response to this HPV type, with response levels to this HPV type similar to levels in subjects without prior HPV vaccination.

Table 26 Month 7 anti-HPV GMTs in prior qHPV vaccine recipients and subjects with no prior HPV vaccination who received a 3 dose regimen of 9vHPV vaccine

Assay	9vHPV vaccine								
	Prior qHPV vaccine recipients[a]						No prior HPV vaccination[b]		
	Females 12–15 years of age (*N* = 120)			Females 16–26 years of age (*N* = 495)			Females 16–26 years of age (*N* = 6792)		
	n	GMT mMU/mL	95% CI	*n*	GMT mMU/mL	95% CI	*n*	GMT mMU/mL	95% CI
Anti-HPV 6	98	3208.7	(2732.5, 3767.9)	413	2020.0	(1865.5, 2187.2)	3993	893.1	(871.7, 915.1)
Anti-HPV 11	100	2747.1	(2316.6, 3257.7)	415	1652.6	(1528.3, 1786.9)	3995	666.3	(649.6, 683.4)
Anti-HPV 16	100	16,122.5	(13,777.5, 18,866.6)	415	10,250.6	(9446.2, 11,123.5)	4032	3131.1	(3057.1, 3206.9)
Anti-HPV 18	100	3646.6	(2885.9, 4607.9)	415	2042.5	(1832.2, 2277.0)	4539	804.6	(782.7, 827.1)
Anti-HPV 31	100	423.4	(350.4, 511.7)	415	231.1	(209.1, 255.5)	4466	658.4	(636.7, 680.9)
Anti-HPV 33	100	256.2	(219.6, 298.7)	415	159.9	(146.9, 174.0)	4702	415.9	(405.6, 426.4)
Anti-HPV 45	100	147.8	(120.8, 180.9)	415	88.1	(80.7, 96.2)	4792	252.8	(246.2, 259.6)
Anti-HPV 52	100	395.3	(334.4, 467.2)	415	239.7	(220.2, 260.8)	4455	379.7	(371.6, 388.0)
Anti-HPV 58	100	425.1	(370.2, 488.2)	415	241.7	(222.8, 262.2)	4486	482.5	(469.9, 495.3)

[a] Girls and women 12–26 years of age enrolled in this study (protocol V503-006; NCT# NCT01047345).
[b] Girls and women 16–26 years of age enrolled in the pivotal efficacy study of 9vHPV vaccine (protocol V503-001; NCT# NCT00543543) [27].
N: number of individuals randomized to the respective vaccination group who received at least one vaccination; *n*: number of individuals contributing to the analysis; GMT: geometric mean titer; mMU: milliMerck units; CI: confidence interval; qHPV vaccine: quadrivalent human papillomavirus (types 6, 11, 16, 18) vaccine; 9vHPV vaccine: 9-valent human papillomavirus (types 6, 11, 16, 18, 31, 33, 45, 52, 58) vaccine.

There are several limitations to this study. The primary objective of the study was to assess the safety profile of the 9vHPV vaccine in prior qHPV vaccine recipients. Clinical efficacy of the 9vHPV vaccine in that population was not studied. Also, because the qHPV vaccine was first licensed in 2006 and the current study started in 2010, no subjects who completed qHPV vaccination more than 4 years prior to the first dose of 9vHPV vaccine were available for study. Nonetheless, the immunogenicity results (which appear determined by immune memory to the prior qHPV vaccination) may conceivably remain applicable beyond 4 years, since immune memory to qHPV vaccination persists for a longer time, as previously reported.

The authors concluded that administration of a 3-dose regimen of 9vHPV vaccine to adolescent girls and young women 12–26 years of age who are prior qHPV vaccine recipients is highly immunogenic with respect to HPV types 31/33/45/52/58 and generally well tolerated.

Medsafe comments

This study provides useful information for anyone who has completed a course of Gardasil and wishes to use Gardasil 9 vaccine. Also of interest from the safety perspective is the comparison of adverse events with a saline placebo. Notably the high rate of systemic adverse events in the placebo group.

3.3.6 Protocol V503-007 assessed the effect of co-administration with Repevax [12]

This was an open-label randomised multicentre study. 1054 male and female subjects aged 11 to 15 were assigned to receive Repevax (diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis) on day 1 or month 1 with 3 dose Gardasil 9. Non-inferiority of anti-HPV GMTs and seroconversion rates for all 9vHPV antigens were demonstrated for the concomitant group compared to the non-concomitant group. For Repevax non-inferiority of immune response was established for all components for both groups.

It was concluded that the two vaccines could be administered together.

3.3.7 Protocol V503-009/GDS01C: Non-inferior immunogenicity (HPV 16 and 18) of 9vHPV versus qHPV in girls 9-15 years. [13]

The authors compared the immunogenicity and safety of the 9vHPV vaccine versus the qHPV vaccine in 9-15 year old girls.

Participants (n = 600) were randomized to receive 9vHPV or qHPV vaccines on day 1, month 2 and month 6. Serology testing was performed on day 1 and month 7. HPV type-specific antibody titres

were expressed as geometric mean titres and seroconversion rates. Vaccine safety was also assessed.

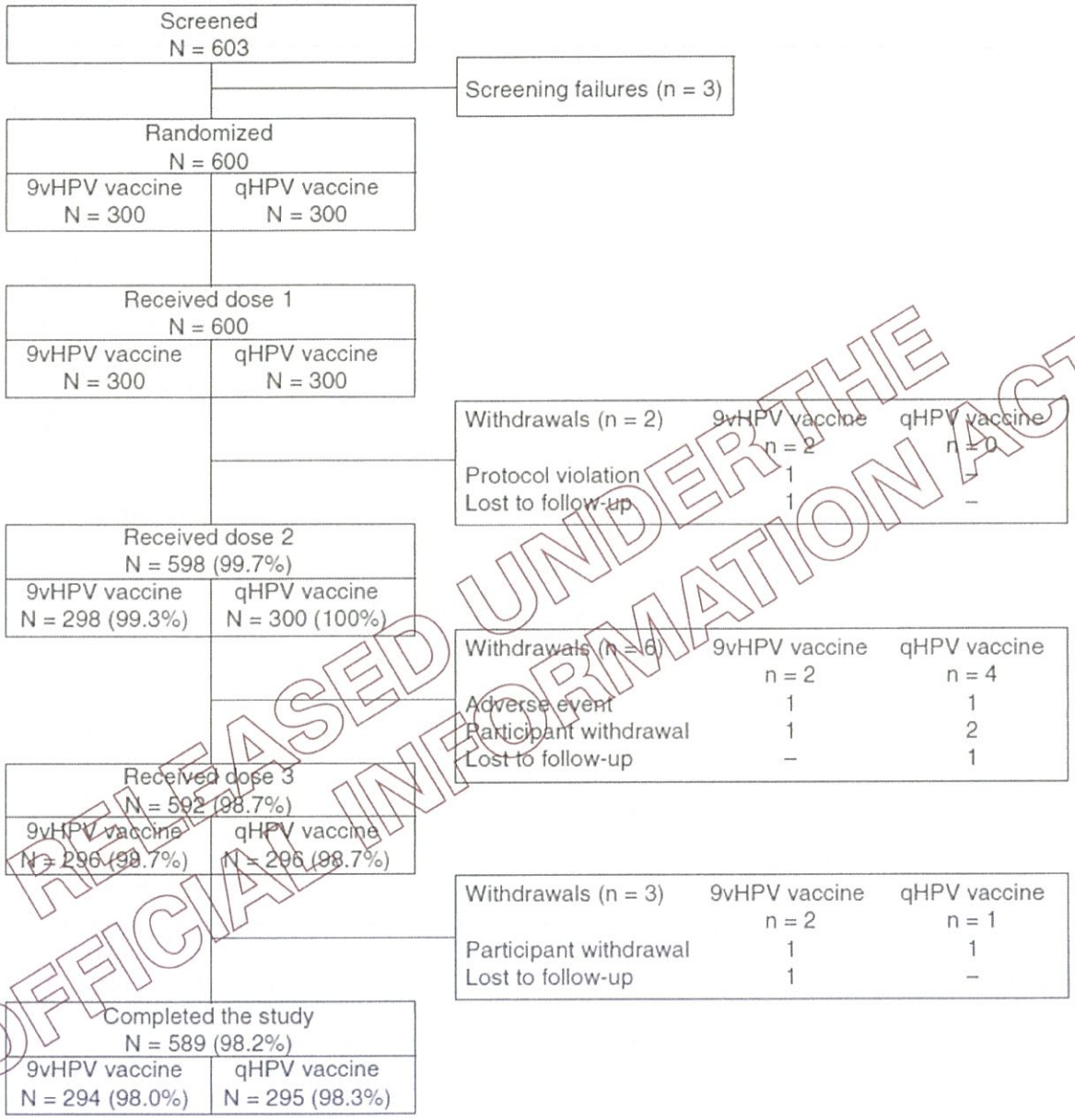


Figure 10 Disposition of subjects

The HPV 6/11/16/18 immune responses elicited by the 9vHPV vaccine were comparable with those elicited by the qHPV vaccine. All participants (except 1 for HPV 45) receiving the 9vHPV vaccine seroconverted for HPV 31/33/45/52/58. The 9vHPV and qHPV vaccines showed comparable safety profiles, although the incidence of injection-site swelling was higher in the 9vHPV vaccine group.

In addition to immune responses to HPV 31/33/45/52/58, a 3-dose regimen of the 9vHPV vaccine elicited a similar immune response to HPV 6/11/16/18 when compared with the qHPV vaccine in girls aged 9–15 years. The safety profile was also similar for the 2 vaccines.

Most participants experienced at least 1 AE during the study. Vaccine-related AEs were reported for 93.3% of participants receiving the 9vHPV vaccine and 90.3% of participants receiving the qHPV vaccine from day 1 to month 7.

Table 27 Summary and comparison of post dose 3 anti HPV GMTs (Per-Protocol Set) [13]

Assay (cLIA)	Seropositivity cut-off value (mMU/mL)	9vHPV Vaccine n	9vHPV Vaccine GMT (mMU/mL)	9vHPV Vaccine 95% CI	qHPV Vaccine n	qHPV Vaccine GMT (mMU/mL)	qHPV Vaccine 95% CI	Estimated GMT Ratio 9vHPV/ qHPV (95% CI)
Anti-HPV 16	20							
All		276	6739.5	6134.5–7404.1	270	6887.4	6220.8–7625.5	0.97 (0.85–1.11)*
9–12 yr		137	8143.7	7136.1–9293.5	131	8426.8	7346.1–9666.3	0.97 (0.80–1.17)
13–15 yr		139	5592.6	4920.6–6356.3	139	5695	4930.8–6577.7	0.98 (0.81–1.19)
Anti-HPV 18	24							
All		276	1956.6	1737.3–2203.7	269	1795.6	1567.2–2057.3	1.08 (0.91–1.29)*
9–12 yr		137	2475.5	2117.5–2894.0	131	2474.1	2065.8–2963.0	1.00 (0.79–1.27)
13–15 yr		139	1551.8	1306.3–1843.5	138	1324.6	1094.3–1603.5	1.17 (0.91–1.51)
Anti-HPV 6	30							
All		273	1679.4	1518.9–1856.9	261	1565.9	1412.2–1736.3	1.07 (0.93–1.23)
9–12 yr		135	2013.2	1770.0–2289.8	129	1919.8	1673.0–2203.1	1.05 (0.87–1.26)
13–15 yr		138	1406.5	1211.3–1633.2	132	1283.2	1107.1–1487.2	1.10 (0.89–1.35)
Anti-HPV 11	16							
All		273	1315.6	1183.8–1462.0	261	1417.3	1274.2–1576.5	0.93 (0.80–1.08)
9–12 yr		135	1571.6	1375.5–1795.6	129	1662.6	1437.8–1923.5	0.95 (0.78–1.15)
13–15 yr		138	1105.5	942.7–1296.4	132	1212.6	1041.1–1412.3	0.91 (0.73–1.14)
Anti-HPV 31	10							
All		276	1770.4	1585.7–1976.6	268	22.2	18.9–26.1	—
9–12 yr		137	2111.8	1818.1–2452.9	131	28.4	22.5–35.8	—
13–15 yr		139	1488	1270.5–1742.7	137	17.5	14.0–21.9	—
Anti-HPV 33	8							
All		275	937.1	845.3–1038.9	269	4	3.6–4.5	—
9–12 yr		136	1088.1	941.9–1257.1	131	4.8	4.0–5.7	—
13–15 yr		139	809.7	700.6–935.8	138	3.1	2.6–3.8	—
Anti-HPV 45	8							
All		275	622.4	545.4–710.2	271	3.2	2.8–3.6	—
9–12 yr		137	728.8	605.4–877.4	132	3.9	3.2–4.6	—
13–15 yr		138	532.1	441.6–641.1	139	2.7	2.3–3.2	—
Anti-HPV 52	8							
All		276	927.3	837.5–1026.9	269	1.9	1.8–2.1	—
9–12 yr		137	1092.1	951.2–1254.0	131	1.9	1.8–2.1	—
13–15 yr		139	799.3	681.7–913.8	138	1.9	1.7–2.1	—
Anti-HPV 58	8							
All		267	1348.9	1218.3–1493.2	261	9.4	8.1–10.9	—
9–12 yr		130	1538.7	1310.3–1760.4	128	12.8	10.3–15.9	—
13–15 yr		137	1190.3	1027.0–1379.3	133	7	5.8–8.4	—

*Noninferiority was achieved as the lower limit of the 2-sided 95% CI for the GMT ratio was greater than 0.67. The estimated GMT ratio and associated CI are based on an analysis of variance model including group and age stratum as independent variables.
CI, confidence intervals; cLIA, competitive Luminex immunoassay; n, number of participants with available data; qHPV types are 6/11/16/18.

Medsafe comment

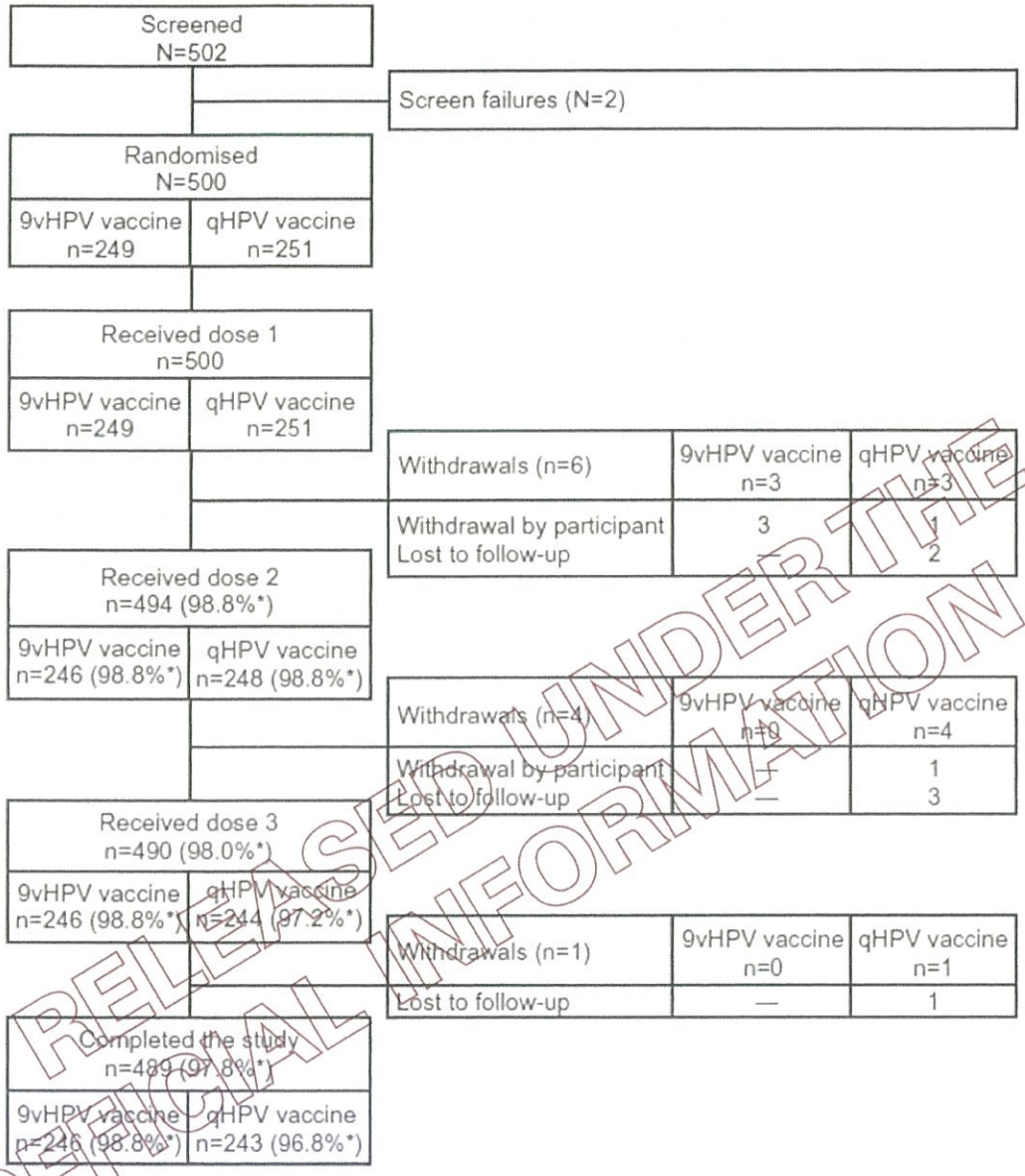
This study showed adequate generation of an immune response in the younger age group.

3.3.8 Comparability study of immunogenicity and safety of 9vHPV compared to qHPV in men.[9]

Participants (N = 500) were randomised to receive 9vHPV or qHPV vaccines on day 1, month 2 and month 6. Serology testing was performed on day 1 and month 7. HPV type-specific antibody titres (anti-HPV 6/11/16/18/31/33/45/52/58) were determined by competitive Luminex immunoassay and expressed as geometric mean titres and seroconversion rates. Vaccine safety was also assessed.

The HPV 6/11/16/18 immune responses elicited by the 9vHPV vaccine were comparable with those elicited by the qHPV vaccine. All participants receiving the 9vHPV vaccine seroconverted for HPV 31/33/45/52/58. The 9vHPV and qHPV vaccines showed comparable safety profiles.

In addition to immune responses to HPV 31/33/45/52/58, a three-dose regimen of the 9vHPV vaccine elicited a similar immune response to HPV 6/11/16/18 when compared with the qHPV vaccine in men aged 16–26 years.



*Percentages are calculated based on the number of randomised participants

Figure 11 Disposition of subjects

The safety profile was also similar for the two vaccines.

The authors consider that results from this study support extending the efficacy findings with qHPV vaccine to 9vHPV vaccine in men aged 16–26 years.

Table 28 Summary of month 7 GMTs in the 9vHPV and qHPV vaccine groups

Assay	9vHPV vaccine *N* = 249			qHPV vaccine *N* = 251			Estimated GMT ratio 9vHPV/qHPV (95% CI)
	n	GMT (mMU/mL)	95% CI	*n*	GMT (mMU/mL)[a]	95% CI[a]	
Anti-HPV 6							
All	228	758.3	665.9; 863.4	226	618.4	554.0; 690.3	1.23 (1.04; 1.45)[b]
16–17 y	36	1284.5	1009.0; 1635.2	36	1012.7	794.0; 1291.6	
18–26 y	192	686.9	594.8; 793.2	190	563.2	500.2; 634.2	
Anti-HPV 11							
All	228	681.7	608.9; 763.4	226	769.1	683.5; 865.3	0.89 (0.76; 1.04)[b]
16–17 y	36	1138.6	889.4; 1457.5	36	1119.3	859.7; 1457.2	
18–26 y	192	619.2	548.1; 699.7	190	716.3	629.3; 815.3	
Anti-HPV 16							
All	234	3924.1	3513.8; 4382.3	237	3787.9	3378.4; 4247.0	1.04 (0.89; 1.21)[b]
16–17 y	36	5868.0	4486.1; 7675.6	37	6045.7	4445.0; 8222.9	
18–26 y	198	3647.2	3237.5; 4108.7	200	3474.0	3079.9; 3918.6	
Anti-HPV 18							
All	234	884.3	766.4; 1020.4	236	790.9	683.0; 915.7	1.12 (0.91; 1.37)[b]
16–17 y	36	1390.4	989.6; 1953.6	36	1346.2	951.1; 1905.4	
18–26 y	198	814.5	696.9; 951.8	200	718.7	613.1; 842.3	
Anti-HPV 31							
All	234	794.4	694.2; 909.2	237	14.8	12.5; 17.5	
16–17 y	36	1441.9	999.1; 2080.9	36	22.0	13.8; 35.1	
18–26 y	198	712.8	619.1; 820.8	201	13.8	11.5; 16.5	
Anti-HPV 33							
All	236	460.5	410.6; 516.4	236	3.4	3.1; 3.7	
16–17 y	36	778.8	586.0; 1035.1	37	4.4	3.4; 5.7	
18–26 y	200	418.9	371.0; 473.1	199	3.2	2.9; 3.5	
Anti-HPV 45							
All	232	262.9	226.2; 305.5	236	2.5	2.3; 2.8	
16–17 y	34	479.1	321.9; 713.3	37	3.1	2.4; 4.0	
18–26 y	198	237.1	202.3; 278.1	199	2.4	2.1; 2.6	
Anti-HPV 52							
All	235	430.7	377.8; 491.0	236	1.9	1.8; 2.1	
16–17 y	36	773.6	551.7; 1084.7	37	2.5	2.0; 3.1	
18–26 y	199	387.4	337.1; 444.8	199	1.9	1.7; 2.0	
Anti-HPV 58							
All	232	691.0	614.9; 776.5	233	5.7	5.0; 6.5	
16–17 y	35	1259.1	938.1; 1690.1	36	9.0	6.0; 13.4	
18–26 y	197	621.1	549.8; 701.8	197	5.2	4.6; 6.0	

CI, confidence interval; GMT, geometric mean titres; mMU, milli-Merck units; *N*, number of randomised participants in the respective vaccination group; *n*, number of participants contributing to the analysis; y, years.

[a] The estimated GMT ratio and associated CI are based on an analysis of variance (ANOVA) model including group and age strata as independent variables.

[b] Non-inferiority was achieved if the lower bound of the 2-sided 95% CI for the GMT ratio was greater than 0.50.

Medsafe comments

This study provides further support for use in men.

3.4 Two dose schedule

3.4.1 Limitations

- Antibody persistence studies have shown that in young adolescent girls a 2-dose regimen can result in lower HPV antibody responses than a 3-dose regimen for some HPV types several years after vaccination.

There is a possibility that that the GMT ratios for girls (2-dose)/women (3-dose) may decrease with time. If protection of a two-dose schedule only lasts for ten years, the number of prevented cervical cancer cases almost doubles with a three-dose schedule.

- Vaccine effectiveness was assessed using genital warts as the endpoint. The 2-dose regimen was as effective as the 3-dose regimen if the interval between the 2 doses was more than 5 months. It was less effective than the 3-dose regimen if the interval between the 2-doses was 4 months or less.

While efficacy of qHPV was initially established in women aged 16 to 26 years old, bridging with immunogenicity data was used for preadolescents and adolescents.

3.4.2 Study V503-010: Comparison of antibody responses to 2 doses of 9vHPV in children 9-14 years of age compared to 3 doses in women aged 16 to 26 years

This same immune-bridging strategy (demonstration of non-inferior antibody responses in girls and boys compared to the antibody response in women who were protected from Cervical, Vulvar, or Vaginal HPV Lesions) was the basis of licensure of a 3-dose regimen in girls and boys, 9 to 15 years of age, for both the qHPV and 9vHPV vaccines.

In study V503-010 study, immunogenicity was compared for the following groups:

Girls and boys 9 to 14 years of age

- 2-dose regimens (2 doses separated by a 6-month interval; the '2-dose [0, 6] regimen')
- 2 doses separated by a 12-month interval; the '2-dose [0, 12] regimen')
- 3-dose (0, 2, 6) regimen (exploratory analyses).

Young women 16 to 26 years of age

- 3-dose (0, 2, 6) regimen.

The study will continue for evaluation of persistence of antibody responses through Month 36.

Immunogenicity analyses were conducted in the per-protocol immunogenicity (PPI) population. The per-protocol immunogenicity (PPI) population consisted of individuals who were

- seronegative at Day 1 to the relevant HPV type(s),
- received all planned vaccinations within pre-specified time intervals,
- provided serology result 4 weeks post last dose of the assigned regimen, and
- did not deviate from the study protocol in ways that could interfere with vaccine effect.

One-sided 2.5% significance level was used for the calculations. The power and sample size were calculated based on the following assumptions:

1) the exclusion rates for PPI population were approximately 20% for the 9 to 14 year old girls and boys group and 30% for the 16 to 26 year old young women,

2) a standard deviation (SD) of the natural-log-transformed titres is 1.2, and

3) non-inferiority margin for GMT ratio is 1.5 fold.

The estimates of exclusion rates and standard deviation are based on data from previous qHPV vaccine studies.

The statistical criterion for non-inferiority with respect to GMT required that the lower bound of the 95% CI for the GMT ratio (girls/young women and boys/young women) be >0.67 for each HPV type.

For each HPV type, the hypotheses to be tested were

H0: GMT1/GMT2 ≤ 0.67,

Ha: GMT1/GMT2 > 0.67

Where GMT1 refers to those receiving the two-dose regimen, and GMT2 refers to GMTs at 4 weeks post-dose 3 for those receiving the three dose (0, 2, 6) regimen.

Among the 1,518 randomized subjects, a total of 44 subjects (2.9%) discontinued from the study during the vaccination period (Day 1 through Month 7 for subjects who received the [0, 6] or [0, 2, 6] regimens, Day 1 through Month 13 for subjects who received the [0, 12] regimen).

Most subjects who discontinued prior to the end of the vaccination period were lost to follow-up or withdrew consent.

The non-inferiority hypothesis relating to the 2 dose regimen was successfully demonstrated.

Table 29 Statistical analysis of non-inferiority comparing the 2 dose regimen with the three dose regimen

	Girls, 9 to 14 years 2 Doses (0, 6) (N = 301)		Girls, 9 to 14 years 2 Doses (0, 12) (N = 150)		Girls, 9 to 14 years 3 doses (0, 2, 6) (N=300)		GMT Ratio* (95% CI)	
Anti-HPV Type	n	Estimated GMT mMU/mL	n	Estimated GMT mMU/mL	n	Estimated GMT mMU/mL	Girls (0,6) / Girls (3 doses)	Girls (0, 12) / Girls (3 doses)
HPV 6	258	1,657 9	123	2,685 7	254	1,496 1	1 11 (0 94, 1 30)	1 80 (1 44, 2 23)
HPV 11	258	1,338 9	123	2,915 9	254	1,306 3	1 06 (0 90, 1 25)	2 23 (1 82, 2 74)
HPV 16	272	8,001 9	129	13,828 1	269	6,996 0	1 14 (0 98, 1 34)	1 98 (1 62, 2 41)
HPV 18	273	1,872 8	129	2,696 0	270	2,049 3	0 91 (0 77, 1 09)	1 32 (1 05, 1 65)
HPV 31	272	1,436 3	132	2,086 4	271	1,748 3	0 82 (0 69, 0 97)	1 19 (0 96, 1 48)
HPV 33	273	1,030 0	132	2,037 4	275	796 4	1 29 (1 10, 1 52)	2 56 (2 10, 3 11)
HPV 45	274	357 6	132	439 6	275	661 7	0 54 (0 45, 0 65)	0 66 (0 53, 0 84)
HPV 52	272	581 1	131	1,028 2	275	909 9	0 64 (0 55, 0 75)	1 13 (0 93, 1 37)
HPV 58	270	1,251 2	129	2,244 7	273	1,229 3	1 02 (0 87, 1 20)	1 83 (1 49, 2 23)

†(0, 6) regimen: vaccination at Day 1 and Month 6; (0, 12) regimen: vaccination at Day 1 and Month 12; (0, 2, 6) regimen: vaccination at Day 1, Month 2, and Month 6

* Includes all subjects who (1) received all planned vaccinations within acceptable day ranges, (2) had 4 weeks post last dose serum sample collected within an acceptable day range, (3) were seronegative at Day 1 for the relevant HPV type(s), and (4) had no other protocol violations that could interfere with the evaluation of immune response

N = Number of individuals randomized to the respective vaccination group who received at least one vaccination

n = Number of individuals contributing to the analysis.

CI = confidence interval; cLIA = competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = milli-Merck units

Source: Table 11-16 and Table 11-17 from [Ref 5.3.5.4: P010]

For HPV types 31, 45 and 52, GMTs one month after the last dose were lower in girls who received the 2-dose (0, 6) regimen than in girls who received the 3-dose regimen, with point estimates for the

GMT ratio (2-dose/3-dose) between 0.54 and 0.82, and upper limits of the 95% CI of the GMT ratio of < 1.

For HPV type 45, the GMT one month after the last dose was lower in girls who received the 2-dose (0, 12) regimen than in girls who received the 3-dose regimen, with a point estimate for the GMT ratio (2-dose/3-dose) of 0.66 and the upper limit of the 95% CI of the GMT ratio of <1.

Given that seroconversion rates were almost 100% for each HPV type among 9 to 14 year old girls, for 2-dose and 3-dose regimens, there are no notable differences in seroconversions between 2-dose and 3-dose regimens.

Medsafe comments
The 0, 12 month 2 dose regimen was better than the 0, 6 regimen. The GMT for one HPV type – 45 were lower than for the three dose regimen. However, given that a lower level for antibody efficacy has not been established there is no evidence that this lower level for HPV45 will be associated with reduced efficacy. The long-term persistence of antibodies after a two dose regimen has yet to be determined.

3.5 Safety information for Gardasil 9

3.5.1 Preclinical data

Non-clinical safety studies included an intramuscular repeat-dose toxicity study in rats (with local tolerance and non-GLP immunogenicity assessments), an intramuscular developmental toxicity and immunogenicity study in rats with fertility and prenatal evaluation, and an intramuscular developmental toxicity and immunogenicity study in rats with fertility and postnatal evaluation.

There were no treatment-related effects on mating performance, fertility, or embryonic/fetal survival. No treatment-related changes were observed upon gross examination of the vaccinated females. There was no evidence of treatment-related effects on embryonic/fetal viability, fetal weights, sex ratios, and external, visceral, coronal, and skeletal morphology.

3.5.2 Clinical trials [14]

The overall safety profile of the 9-valent human papillomavirus (9vHPV) vaccine was evaluated across 7 Phase III studies, conducted in males and females (non-pregnant at entry), 9 to 26 years of age.

More than 15 000 subjects received ≥1 dose of 9vHPV vaccine. In 2 of the studies, >7000 control subjects received ≥1 dose of quadrivalent HPV (qHPV) vaccine. Serious and non-serious adverse events (AEs) and new medical conditions were recorded throughout the study. Subjects testing positive for pregnancy at day 1 were not vaccinated; those who became pregnant after day 1 were discontinued from further vaccination until resolution of the pregnancy. Pregnancies detected after study start (n = 2950) were followed to outcome.

Table 30 Phase III studies of 9vHPV vaccine contributing to the combined safety analysis

Study	Key Objectives	Safety Population	Vaccination	Duration of Safety Follow-up
001	Immunogenicity, efficacy vs qHPV	Women aged 16–26 y (*N* = 14 185)	9vHPV *N* = 7092 [a] qHPV *N* = 7093	Up to 72 mo[b]
002	Adult-to-adolescent immunobridging	Girls (*n* = 1933) and boys (*n* = 666) aged 9–15 y; women aged 16–26 y (*n* = 467)	9vHPV *N* = 3066	Girls/boys 36 mo, women 12 mo
003	Women to men immunobridging	Men (*n* = 1416) and women (*n* = 1099) aged 16–26 y	9vHPV *N* = 2515	12 mo
005	Concomitant use Menactra/ Gardasil	Girls (*n* = 620) and boys (*n* = 617) aged 11–15 y	9vHPV *N* = 1237	7 mo
006	Assessment in previous qHPV vaccine recipients	Girls aged 12–15 y (*n* = 120), women aged 16–26 y (*n* = 493)	9vHPV *N* = 613[c]	7 mo
007	Concomitant use Repevax	Girls (*n* = 526) and boys (*n* = 526) aged 11–15 y	9vHPV *N* = 1052	7 mo
009	qHPV-to-9vHPV immunobridging	Girls aged 9–15 y (*N* = 598)	9vHPV *N* = 300 qHPV *N* = 298	7 mo

Study 001 (NCT00543543, protocol V503-001)[8] Study 002 (NCT00943722, protocol V503-002)[9] Study 003 (NCT01651949, protocol V503-003)[10] Study 005 (NCT00988884, protocol V503-005)[11] Study 006 (NCT01047345, protocol V503-006)[12] Study 007 (NCT01073293, protocol V503-007)[13] Study 009 (NCT01304498, protocol V503-009/GDS010) [a] *N/n* = subjects who received at least 1 vaccination and did not receive a mixed vaccine regimen. A total of 15 875 subjects received at least 1 vaccination in these studies. Most subjects (97.2%, 15 427 of 15 875) received the 3 vaccinations.

[a] Subjects who received the low-dose or high dose formulation of 9vHPV vaccine during the dose selection portion of the study[8, 14] are not considered in this report; safety findings in these subjects are reported in Luxembourg et al.[15]

[b] Visit cutoff date: March 10, 2014; maximum follow-up 72 mo after vaccination dose 1 (median: 48 mo).

[c] Subjects who received placebo in Study 006 are not considered in this report; safety findings in these subjects are reported.[12]

All subjects received a Vaccination Report Card (VRC) at each vaccination visit. Subjects were asked to record their oral temperature on the VRC in the evening after each vaccination and daily thereafter for 4 days. Injection site and systemic AEs were recorded on the VRC for a total of 15 days including the day of vaccination. The VRC prompted the recording of injection-site AEs of pain, swelling, and erythema for 5 days including the day of vaccination.

Investigators were instructed to assign causality to AEs on the basis of exposure, time course, likely cause, and consistency with the vaccine's known profile. Vaccine-related AEs were those that were determined by the investigator to be possibly, probably, or definitely vaccine related.

New medical events occurring outside a day 1 to 15 post-vaccination period and not reported as serious AEs were reported as new medical conditions. New medical conditions were collected at

each scheduled visit for the entire duration of the studies; collection of new medical condition data were pre-specified in the study protocols and was mandatory.

Table 31 Subject characteristics

	9vHPV Vaccine
Subjects in population, *n*	15875
Sex, *n* (%)	
Male	3225 (20.3)
Female	12650 (79.7)
Age, *n* (%)	
9–15 y	5308 (33.4)
16–17 y	608 (3.8)
18–26 y	9959 (62.7)
Mean (SD)	18.4 (5.1)
Median (range)	20.0 (9–26)
Race, *n* (%)	
Asian	2213 (13.9)
Black	718 (4.5)
Other[a]	3628 (22.9)
White	9316 (58.7)
Region[b]	
Africa	215 (1.4)
Asia-Pacific	2112 (13.3)
Europe	5660 (35.7)
Latin America	4186 (26.4)
North America	3702 (23.3)

[a] Mostly multiracial subjects.

[b] Study participants were from 31 countries (Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, Costa Rica, Denmark, Finland, Germany, Hong Kong, India, Israel, Italy, Japan, Korea, Malaysia, Mexico, New Zealand, Norway, Peru, the Philippines, Poland, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, and the United States [including Puerto Rico]).

The most common AEs (≥5%) experienced by 9vHPV vaccine recipients were injection-site AEs (pain, swelling, erythema) and vaccine-related systemic AEs (headache, pyrexia).

Injection-site AEs were more common in 9vHPV vaccine than qHPV vaccine recipients; most were mild-to-moderate in intensity.

Discontinuations and vaccine-related serious AEs were rare (0.1% and <0.1%, respectively).

Seven deaths were reported; none were considered vaccine related.

The proportions of pregnancies with adverse outcome were within ranges reported in the general population.

Twenty subjects (0.1%) discontinued vaccination because of an AE.

A total of 356 subjects (2.3%) who received 9vHPV vaccine reported serious AEs including 51 (0.3%) who reported serious AEs from day 1 to 15 after any vaccination.

The most common serious AEs were elective abortions, spontaneous abortions, and appendicitis; other serious AEs were of low frequency and affected various system organ classes.

Only 1 AE of anaphylaxis was reported, due to a non-study medication.

Table 32 Adverse event summary

	9vHPV Vaccine					
	All (*N* = 15776)		Female Subjects (*n* = 12583)		Male Subjects (*n* = 3193)	
	Count	%	Count	%	Count	%
With ≥1 AEs[a]	14295	90 6	11660	92 7	2635	82 5
Injection site event[c]	13372	84 8	11085	88 1	2287	71 6
Pain	13118	83 2	10937	86 9	2181	68 3
Mild	8068	51 1	6480	51 5	1588	49 7
Moderate	4497	28 5	3942	31 3	555	17 4
Severe	552	3 5	514	4 1	38	1 2
Unknown	1	0 0	1	0 0	0	0 0
Swelling	5698	36 1	4918	39 1	780	24 4
Mild (0 to ≤2 5 cm)	3914	24 8	3348	26 6	566	17 7
Moderate (>2 5 to ≤5 0 cm)	1158	7 3	1036	8 2	122	3 8
Severe (>5 0 cm)	618	3 9	526	4 2	92	2 9
Unknown	8	0 1	8	0 1	0	0 0
Erythema	4859	30 8	4145	32 9	714	22 4
Mild (0 to ≤2 5 cm)	3896	24 7	3304	26 3	592	18 5
Moderate (>2 5 to ≤5 0 cm)	698	4 4	611	4 9	87	2 7
Severe (>5 cm)	251	1 6	216	1 7	35	1 1
Unknown	14	0 1	14	0 1	0	0 0
Pruritus	636	4 0	534	4 2	48	1 5
Mild	487	3 1	454	3 6	33	1 0
Moderate	138	0 9	130	1 0	8	0 3
Severe	11	0 1	10	0 1	1	0 0
Systemic event[c]	8188	51 9	6772	53 8	1411	44 2
Vaccine-related[d] systemic event	4217	26 7	3500	27 8	717	22 5
Headache	2090	13 2	1765	14 0	325	10 2
Pyrexia	955	6 1	734	5 8	221	6 9
Nausea	503	3 2	451	3 6	52	1 6
Dizziness	455	2 9	417	3 3	38	1 2
Fatigue	294	1 9	249	2 0	45	1 4
Serious event[a]	356	2 3	310	2 5	46	1 4
Vaccine-related[d] event	7	0 0	6	0 0	1	0 0
Death	7	0 0	7	0 1	0	0 0
Discontinuation[e] because of an AE	20	0 1	15	0 1	5	0 2
Because of a vaccine-related[d] event	16	0 1	11	0 1	5	0 2
Because of a serious event	5	0 0	4	0 0	1	0 0
Because of a serious vaccine-related[d] event	2	0 0	1	0 0	1	0 0

Injection site and systemic AEs shown are those with incidence ≥2% in any vaccination group during the study. *N/n* = Number of subjects as treated who received at least 1 dose of the indicated vaccine and had at least 1 follow-up visit for an AE

[a] At any time during the study

[b] Days 1 to 5 after any vaccination visit

[c] Days 1 to 15 after any vaccination visit

[d] As determined by the reporting investigator

[e] Study vaccination withdrawn

The 7 serious AEs considered related to the vaccine by the investigator were.

1. Allergic reaction 3 hours after dose 1, patient self-treated and recovered the same day. No further doses given.
2. Patient with history of allergy and asthma experienced an asthmatic crisis one day after dose 1. He was hospitalised and recovered the next day. No further doses given.
3. Tonsillitis 2 days after dose 1. Treated with antibiotics and recovered 5 days later, completed the course.
4. Fever, pain headache and malaise 11 hours after dose 3, recovered the next day.
5. Severe headache after dose 3 with fever and neck stiffness hospitalised for 2 days. Bitten by spider 5 days before dose 3 and was being treated for infected spider bite at dose 3.
6. Hypersomnia 4.3 years after dose 3.
7. POTS 3.8 years after dose 3.

The 7 deaths were described as follows.

1. 21 year-old female committed suicide 15 days after dose 1

2. 17 year old female diagnosed with acute B cell lymphoblastic leukaemia 27 days after dose 3, died 862 days after the initial diagnosis.
3. 20 year-old female involved in a car accident 226 days after dose 3, died at the scene.
4. 15 year old female diagnosed with myeloid leukaemia at enrolment. Died of sepsis 559 days after dose 3, 7 days after the start of second round of chemotherapy.
5. 23 year old female experienced abdo pain 531 days after dose 3 and died the next day. On autopsy it was noted that the cause of death was hypovolemic shock and septic shock; findings included diffuse haemorrhage and necrosis of the jejunum and ileum, intestinal adhesions, volvulus, and intestinal strangulation. It was noted that the left ovary had been removed due to a tumour an appendectomy and tubal sterilisation had been performed 59 days after dose 3.
6. 23 year old female died during the night 678 days after dose 3. Diagnosis was sudden unexpected death syndrome.
7. 25 year-old female diagnosed with acute promyelocytic leukaemia 1285 days after dose 3. Died of multiple organ failure and sepsis 8 days after the first round of therapy.

Exploratory analyses of events of potential interest were performed. AEs of syncope occurred in 36 of the 15 776 9vHPV vaccine recipients (0.2%), including 22 cases after dose 1, 11 after dose 2, and 3 after dose 3. Of the 36 cases, 20 occurred on the same day as vaccination. Events occurred mostly in female subjects (94% [34 of 36]), did not cause any discontinuation from vaccination or the study, and did not reoccur after a subsequent dose.

Two subjects in study 001 (1 in each vaccine cohort) were diagnosed with complex regional pain syndrome (CRPS); both cases were attributed to a previous injury. Two subjects who received 9vHPV vaccine were diagnosed with postural orthostatic tachycardia syndrome (POTS), although 1 subject did not have recurrent episodes even after subsequent vaccinations, and the other subject had no temporal association (occurred >3 years after vaccination).

Pregnancy outcomes (including outcomes among live births through the neonatal period, ie, first 6 weeks of life) are shown in Table 34.

Table 33 Summary of outcomes of pregnancies in study 001

	9vHPV Vaccine (*n* = 7092)			qHPV Vaccine (*n* = 7093)		
	Overall	Conception Date[a]		Overall	Conception Date[a]	
		Within 30 d of Vaccination	Not Within 30 d of Vaccination		Within 30 d of Vaccination	Not Within 30 d of Vaccination
No. of subjects with pregnancies	1289	85	1122	1239	88	1172
No. of pregnancies[b]	1482	86	1396	1458	88	1371
No. of pregnancies with known outcome[b]	1459	85	1374	1435	87	1348
Live births (%)						
Number of live births/number of pregnancies with known outcome	1168/1459 (80.1)	42/85 (49.4)	1126/1374 (82.0)	1137/1435 (79.2)	47/87 (54.0)	1090/1348 (80.9)
Normal	1128/1459 (77.3)	40/85 (47.1)	1088/1374 (79.2)	1101/1435 (76.7)	44/87 (50.6)	1057/1348 (78.4)
Abnormal	29/1459 (2.0)	0/85 (0.0)	29/1374 (2.1)	31/1435 (2.2)	2/87 (2.3)	29/1348 (2.2)
Congenital anomaly	23/1459 (1.6)	0/85 (0.0)	23/1374 (1.7)	21/1435 (1.5)	1/87 (1.1)	20/1348 (1.5)
Other abnormality	9/1459 (0.6)	0/85 (0.0)	9/1374 (0.7)	11/1435 (0.8)	1/87 (1.1)	10/1348 (0.7)
Unknown	11/1459 (0.8)	2/85 (2.4)	9/1374 (0.7)	5/1435 (0.3)	1/87 (1.1)	4/1348 (0.3)
Method of delivery						
Cesarean	342/1459 (23.4)	9/85 (10.6)	333/1374 (24.2)	380/1435 (26.5)	14/87 (16.1)	366/1348 (27.2)
Vaginal	826/1459 (56.6)	33/85 (38.8)	793/1374 (57.7)	757/1435 (52.8)	33/87 (37.9)	724/1348 (53.7)
Fetal loss (%)						
Number of fetal losses/number of pregnancies with known outcome	291/1459 (19.9)	43/85 (50.6)	248/1374 (18.0)	298/1435 (20.8)	40/87 (46.0)	258/1348 (19.1)
Type of loss						
Ectopic pregnancy	14/1459 (1.0)	0/85 (0.0)	14/1374 (1.0)	10/1435 (0.7)	1/87 (1.1)	9/1348 (0.7)
Spontaneous abortion	133/1459 (9.1)	17/85 (20.0)	116/1374 (8.4)	159/1435 (11.1)	8/87 (9.2)	151/1348 (11.2)
Late fetal death	4/1459 (0.3)	1/85 (1.2)	3/1374 (0.2)	4/1435 (0.3)	0/87 (0.0)	4/1348 (0.3)
Elective abortion	140/1459 (9.6)	25/85 (29.4)	115/1374 (8.4)	125/1435 (8.7)	31/87 (35.6)	94/1348 (7.0)
Fetal outcome						
Normal	56/1459 (3.8)	11/85 (12.9)	45/1374 (3.3)	48/1435 (3.3)	11/87 (12.6)	37/1348 (2.7)
Abnormal	8/1459 (0.5)	0/85 (0.0)	8/1374 (0.6)	4/1435 (0.3)	0/87 (0.0)	4/1348 (0.3)
Congenital anomaly	6/1459 (0.4)	0/85 (0.0)	6/1374 (0.4)	3/1435 (0.2)	0/87 (0.0)	3/1348 (0.2)
Other abnormality	2/1459 (0.1)	0/85 (0.0)	2/1374 (0.1)	1/1435 (0.1)	0/87 (0.0)	1/1348 (0.1)
Unknown	227/1459 (15.6)	32/85 (37.6)	195/1374 (14.2)	246/1435 (17.1)	29/87 (33.3)	217/1348 (16.1)

n = Number of subjects as treated who received at least 1 dose of the indicated vaccine
[a] Conception date was calculated as date of last menstrual period plus 14 d
[b] A subject may have >1 pregnancy during the study. Each pregnancy is counted in this summary. A pregnancy with multiple fetuses is counted as a single pregnancy, but outcome for each fetus/infant is counted individually

Most pregnancies among 9vHPV vaccine recipients (95.9% [1482 of 1546]) occurred in study 001, which enrolled most of the women of childbearing age and had the longest follow-up.

Most pregnancies resulted in live births (80.1% for 9vHPV and 79.2% for qHPV in study 001) and were largely vaginal deliveries. Elective terminations (in study 001, 9.6% and 8.7% of pregnancies in 9vHPV and qHPV groups, respectively) were due to personal decision except for 9 pregnancies in study 001 (6 in 9vHPV and 3 in qHPV groups), which were terminated because of a congenital anomaly. No elective termination was due to a medical condition in the mother or a perceived risk due to vaccination.

The rate of spontaneous abortions (number of spontaneous abortions per total number of pregnancy outcomes for which an outcome was known) in study 001 was 9.1% in the 9vHPV and 11.1% in the qHPV vaccine groups (rate was 9.2% among all subjects who received 9vHPV vaccine).

Pregnancies with estimated dates of conception (EDC) within 30 days before or after any vaccination were considered to assess whether there could be an underlying high-risk period after conception. Because women were asked to use effective birth control only during the vaccination phase (day 1–month 7), only a small number of the EDC occurred within 30 days before or after a vaccination, representing in study 001 5.8% (85 of 1459) and 6.1% (87 of 1435) in the 9vHPV and qHPV vaccine groups, respectively.

Reported congenital anomalies including anomalies in live infants and fetal anomalies that resulted in elective abortions were diverse and affected various organs; none were considered vaccine related. No congenital anomaly was reported in pregnancies with EDC within 30 days before or after a vaccination with 9vHPV vaccine.

Congenital anomaly rates (<2% of live births) were consistent with prevalences reported in the literature (ie, 3%–4% of all live births) and in the qHPV vaccine and placebo arms of the qHPV vaccine program.

This combined analysis has several limitations. The overall safety database for 9vHPV vaccine is similar in size to that of the pre-licensure database of qHPV vaccine; however, it is insufficiently sized to identify AEs occurring at a rate <1:5200. Such events are expected to be assessed in pharmacovigilance and post-licensure safety analyses.

Because existing HPV vaccines prevent pre-cancers due to HPV 16 and 18, the use of a placebo in subjects not previously vaccinated was deemed unethical. The qHPV vaccine was used as a control in 2 of the studies. Extensive clinical trial and post licensure studies have reinforced the favourable safety profile of the qHPV vaccine in both sexes. The similarity between the safety profile of the 9vHPV vaccine and that of the qHPV vaccine supports the conclusion that the 9vHPV vaccine is generally well tolerated.

The 9vHPV vaccine clinical program was not designed to provide a systematic assessment of the vaccine in pregnant women. Thus, a pregnancy registry for the 9vHPV vaccine has been established in the United States, based on the same process previously established for the pregnancy registry of the qHPV vaccine, to better describe the safety profile of pregnancy exposures to the 9vHPV vaccine.

Medsafe comments

The safety profile appears consistent with that of Gardasil. With regard to the events considered related to Gardasil 9 by the investigator, allergy/hypersensitivity and fever are listed in the data sheet. The tonsillitis was successfully treated with antibiotics and it is unclear why that would be related to vaccination. The headache and neck stiffness appear more likely due to the infected spider bite and the hypersomnia and POTS were diagnosed years after vaccination which therefore seems very unlikely to be a vaccine effect.

Similarly, whilst the deaths are very sad they appear to be due to the usual random causes in this age group. There is no biological plausibility for Gardasil 9 vaccine to cause cancer.

3.5.3 Ongoing safety concerns

The RMP for Gardasil 9 identified the concerns listed in table 35 as ongoing safety concerns.

Table 34 Summary of ongoing safety concerns

Important identified risks	• Hypersensitivity (Type 1)
Important potential risks	• Product confusion between Gardasil and Gardasil®9 • Mixed regimen between Gardasil/ Silgard and Gardasil®9
Missing information	• Long term effectiveness and immunogenicity • Exposure during Pregnancy • Viral type replacement • Immunogenicity and safety in females greater than 26 years of age

3.6 Monitoring and communication

3.6.1 Company activities

Two long-term safety studies are planned. There will be a 10 year follow-up of Scandinavian subjects in study 001 through the Nordic Cancer Registry Programs. In addition, subjects of study 002 will be followed for 10 years post-dose 3.

Pharmacovigilance actions include

- V503-021 Nordic Long-Term Follow-Up Study (10-year extension in subjects from V503-001) for duration of protection and impact on HPV types.
- V503-002-20 Adolescent Long-term Follow-Up Study (10-Year Post-dose 3 Extension) for duration of protection
- Pregnancy Registry in the USA for 5 years

The applicant also proposes a post-marketing immunogenicity and safety study of the 9vHPV vaccine in women 27 to 45 years of age.

Table 35 Additional pharmacovigilance activities to address specific safety concerns or measure the effectiveness of risk minimisation

Study / Activity	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim / Final Reports: (target date:)
Pregnancy Registry (category 3)	To monitor pregnancy outcomes in women exposed to 9vHPV vaccine during pregnancy	Exposure to vaccine during pregnancy	Planned	Interim Reports: 31-AUG-2016 31-AUG-2017 31-AUG-2018 31-AUG-2019 31-AUG-2020 Final Report: ~18 months after enrollment of the last patient
V503-021 Nordic Long-term Follow-Up Study (10-Year extension in subjects from V503-001) (category 3)	To monitor the long-term safety of 9vHPV vaccine To monitor long-term effectiveness and immunogenicity of 9vHPV vaccine To obtain information on duration of effect	▪ Viral type replacement ▪ Long-term Effectiveness Immunogenicity	Planned	Interim Reports: ~4Q2017 ~4Q2019 ~4Q2021 ~4Q2023 Final Report Submission: ~31-Dec-2026
V503-002-20 Adolescent Long-term Follow-Up Study (10-Year Postdose 3 Extension) (category 3)	To monitor long-term effectiveness and immunogenicity of 9vHPV vaccine To obtain information on duration of effect	Long-term Effectiveness Immunogenicity	Planned	Interim 72-Month Report: ~4Q2017 Interim 96 Month Report: ~4Q2019 Final Report Submission: ~31-Mar-2023
A post-marketing immunogenicity and safety study of the 9vHPV vaccine in women 27 to 45 years of age	- To demonstrate immunogenicity for each of the 9 vaccine HPV types in women 27 to 45 years of age - To collect data on the safety profile of 9vHPV vaccine in women 27 to 45 years of age	Immunogenicity and safety in females greater than 26 years of age	Planned	Final Report: ~1Q 2019

3.6.2 Healthcare professional need for information

In a study investigating healthcare professional awareness of Gardasil 9 in the US only around half of the 22 interviewees had heard of Gardasil 9. The study authors note that given that physicians continue to hold misconceptions about 4vHPV, it will be particularly important to address areas of awareness and education regarding 9vHPV. Additionally, there are unmet educational needs among HCPs regarding the new vaccine, specifically regarding safety, side effects, and efficacy. Furthermore, HCPs may also need assistance in anticipating and addressing patient questions.[15]

Table 36 Qualitative themes and exemplar quotes

Concept	Theme	Exemplar quotes
HPV vaccine wareness		
	Aware (n = 12)	"I've heard of it but I haven't gotten a lot of literature about it" "Yes. Can't wait for it to come to my clinics"
	Does not know much (n = 6)	"I might have heard something about it, but I am not terribly familiar with it" "I have [heard of HPV9], but honestly I don't know that much about it"
	Unaware (n = 8)	"No. But honestly I don't even know what the current one is" "I don't think I've heard about anything new regarding any sort of HPV vaccine."
	Heard a rumor (n = 2)	"Vaguely, yes, I've heard rumors"
HCP questions		
	Efficacy (n = 7)	"Just as long as it's equally efficacious and I believe it is"
	Side effects (n = 6)	"Just the adverse side effects for my patients and making sure that they're knowledgeable about it"
	Additional protection (n = 5)	"How much more coverage do you get against all the different types of HPV that cause cervical cancer?"
	Dosing schedule (n = 5)	"Do you have any idea what the recommended dosing schedule for that one is; is it also three vaccinations?"
	Cost (n = 5)	"I'm waiting to see the degree at which cost will impact its availability, so whether that's going to affect our ability to stock it in clinic or whether patients will have the differential coverage for it from their insurers based on whether they're getting the Quadrivalent or Nanovalent"
	General information (n = 5)	"I just want to look at that information myself. I just haven't done it yet" "I don't feel like I know a lot about it right now, so I think that would be the main thing is just getting informed about it"
	Safety (n = 4)	"I guess with vaccines you always – as a provider when you're counseling people on it, you want to make sure you know about safety, side effects, everything"
Anticipated parent/patient questions	Parents will not have questions (n = 14)	"No, I don't think so. I think that they trust in me so that if recommend a vaccine that they know that it is something that their child needs"
	No more than HPV8 questions (n = 4)	R: "I don't know that the 9-valent will have any more questions by parents" INT: "As opposed. . . as compared to the quadrivalent?" R: "Yes" "I don't think it's going to bring up any new questions because it's not a totally new vaccine. It's the same vaccine, just more parts to it because nothing really happened when we switched from 7 to 13 on the pneumococcal. Nobody questions it"
	Lack of scientific understanding (n = 3)	"No. I think for my clinic population I would say no. That's just based on other vaccine modifications that haven't spurred any increase in questions about the strains. I got a lot more questions about Thimerosal and whether that's included versus like the actual, what's included in the vaccine from a scientific standpoint, if that makes any sense"
Possible question topics	Side effects (n = 9)	"If there's any side-effects to worry about. That's usually the biggest one."
	Safety (n = 3)	"I think parents are more concerned about safety than they are even about efficacy and what it prevents and how helpful it is"
	Effectiveness (n = 3)	"I think they'd have the same questions [as the physician], like does it—how well does it work and what are the side effects, how safe is it?"
	Necessity of vaccination (n = 5)	"They'll want to know about how—some of them will ask how long has it been given? Is it necessary? Is it better? Is it—that kind of thing"
	Long-term data (n = 4)	"Probably the same in regards to what would happen if they take this vaccination and potentially what would happen in the next five years after receiving it"

3.6.3 Proposed NZ activities

Given the profile for Gardasil 9 outlined above and the ongoing studies from the sponsor, Medsafe does not consider that any additional studies are necessary in New Zealand.

CARM will closely monitor spontaneous reports for Gardasil 9 and produce monthly reports for Medsafe. These reports will be shared with the Committee.

Medsafe considers that additional communication is necessary and proposes that an article is included in *Prescriber Update* outlining the known profile of Gardasil 9. In addition Medsafe proposes publishing 'questions and answers' on the Medsafe website, similar to those produced for rotavirus vaccine. The pre-market evaluation reports will also be published.

4.0 DISCUSSION AND CONCLUSIONS

Gardasil 9 is a second generation HPV vaccine offering a maximal effectiveness in Australia and New Zealand of 86.5% against cervical cancers, providing it is administered prior to sexual debut. The level of antibodies produced for the HPV strains included in Gardasil is non-inferior and similar levels of antibodies are produced for the other strains, in both boys and girls.

The protective level of antibodies is yet to be determined. In long term follow up of Gardasil vaccines antibody levels drop initially but then plateau suggesting that protection against HPV infection will be long-term. In the Gardasil clinical effectiveness studies subjects were protected from relevant cancer at 8 years, these studies continue.

The two dose regimen appears to provide a similar level of protection to the three dose regimen.

The safety of Gardasil 9 appears to be consistent with Gardasil with a slight increase in injection site reactions and vaccine systemic reactions as expected for a vaccine containing more antigens.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The proposed monitoring and communication is adequate.

6.0 ANNEXES

1. Joura, E.A., et al., A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med, 2015. 372(8): p. 711-23.
2. Van Damme, P., et al., Immunogenicity and Safety of a 9-Valent HPV Vaccine. Pediatrics, 2015. 136(1): p. e28-39.
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4. Schilling, A., et al., Coadministration of a 9-Valent Human Papillomavirus Vaccine With Meningococcal and Tdap Vaccines. Pediatrics, 2015. 136(3): p. e563-72.
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